(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/039451 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/JP02/11639

(22) International Filing Date:
8 November 2002 (08.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PR 8749	8 November 2001 (08.11.2001)	AU
PR 9048	23 November 2001 (23.11.2001)	AU

(71) Applicant *(for all designated States except US)*: **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TSUTSUMI, Hideo** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **TABUCHI, Seiichiro** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **AKAHANE, Atsushi** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **YASUDA, Hironobu** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **OMORI, Hiroki** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **TEMMARU, Kiyoshi** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **ZANKA, Atsuhiko** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(74) Agent: **NOGAWA, Shintaro**; MINAMIMORIMACHI PARK BLDG., 1-3, Nishitenma 5-chome, Kita-ku, Osaka-shi, Osaka 530-0047 (JP).

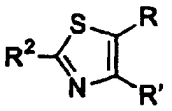
(81) Designated States *(national)*: JP, US.

(84) Designated States *(regional)*: European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

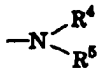
Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

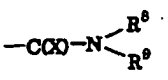
(54) Title: THIAZOLE DERIVATIVE AND PHARMACEUTICAL USE THEREOF



(I)



(i)



(ii)

(57) Abstract: A thiazole derivative of the formula (I):wherein R is a 1-optionally substituted-6-oxo-1,6-dihydro-3-pyridazinyl, R' is an optionally substituted phenyl, and R^2 is hydrogen, a group of the formula (i): wherein R^4 is hydrogen, lower alkyl or lower alkenyl, and R^5 is hydrogen, optionally substituted lower alkyl, acyl, cyclo(lower)alkyl, lower alkenyl, optionally substituted aryl or heterocyclic, or a group of the formula (ii): wherein X is oxygen or sulfur, R^8 is hydrogen or lower alkyl, R^9 is hydrogen, optionally substituted lower alkyl, cyclo(lower)alkyl, lower alkoxy or mono- or di-lower alkylamino or R^8 and R^9 may combine together to form optionally substituted saturated N-containing heterocyclic, or a salt thereof.

WO 03/039451 A2

DESCRIPTION

THIAZOLE DERIVATIVE AND PHARMACEUTICAL USE THEREOF

TECHNICAL FIELD

The present invention relates to a novel thiazole derivative which are useful as medicaments, a process for preparing an intermediate 2-alkyl-6-hydroxy-3(2H)-pyridazinone for their production and a pharmaceutical composition containing the same.

BACKGROUND ART

Adenosine is a ubiquitous biochemical messenger. Adenosine binds to and activates seven-transmembrane spanning G-protein coupled receptors, eliciting a variety of physiological responses. Adenosine receptors are divided into four known subtypes (i. e., A_1, A_{2a}, A_{2b}, and A_3). These receptor subtypes mediate different, and sometimes opposing, effects. Activation of the adenosine A_1 receptor, for example, elicits an increase in renal vascular resistance, while activation of the adenosine A_{2a} receptor elicits a decrease in renal vascular resistance. Accordingly, adenosine antagonists are useful in the prevention and/or treatment of numerous diseases, including cardiac and circulatory disorders, degenerative disorders of the central nervous system, respiratory disorders, and many diseases for which diuretic treatment is suitable.

Some 4-aryl-5-(pyridin-4-yl)thiazole derivatives having adenosine A_3 or A_{2b} inhibitory activities are known (e.g. WO-9964418A, JP-2001-114779A, etc.). However, 4-aryl-5-(6-oxo-1,6-dihydro-pyridazin-3-yl)thiazole derivatives are not known, so far. In addition, any thiazole derivatives having both of adenosine A_1 and A_{2a} inhibitory activities are not known.

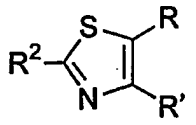
It is known that it is generally difficult to selectively alkylate 3,6-dihydroxypyridazine to give 2-alkyl-6-hydroxy- 3(2H)-pyridazinone (see "Pyridazine" ed. by R. N. Castle, John Wiley & Sons, 1973). For example, 3,6-dihydroxypyridazine is methylated with dimethyl sulfate to give 2-methyl-6-hydroxy- 3(2H)-pyridazinone derivative,

1,2-dimethyl-3(2H), 6(1H)-pyridazinedione and/or 2-methyl-6-methoxy-3(2H)- pyridazinone depending the reaction condition (K. Eichenberger et al., Helv. Chim Acta, 37, 837 (1954)). With diazomethane, 1,3-dihydroxypyridazine is alkylated to give 6-methoxy-3(2H)- pyridazinone (F. Arndt, Angew. Chem., 61, 397 (1949)). With an alkyl halide, 3,6-dihydroxypyridazine is alkylated to give 2-alkyl-6-alkoxy-3(2H), 6(1H)-pyridazinedinone, 2-alkyl-6-hydroxy-3(2H)-pyridazinone or 6-alkoxy-3(2H)-pyridazinone depending the reaction pH condition (R. Sch nbeck, Monatsh Chem., 90, 284 (1959)). Besides, 3,6-dihydroxypyridazine is hardly reactive nor soluble in an usual solvent. R. H. Mizzoni et al reported the preparation of 6-hydroxy-2-alkyl-3(2H)-pyridazinone by reacting maleic anhydride with alkyl hydrazine (J. Amer. Chem. Soc., 76, 2201 (1954)). However, alkylhydrazine is too explosive to prepare or obtain commercially. Therefore, it is desired to develop a safe and convenient process for preparing 2-alkyl-6-hydroxy-3(2H)-pyridazinone, which is useful intermediate for preparing thiazole derivatives.

DISCLOSURE OF INVENTION

The present invention relates to a novel thiazole derivative and a pharmaceutically acceptable salt thereof, which are useful as medicaments; processes for preparing an intermediate 2-alkyl-6-hydroxy-3(2H)-pyridazinone for the production of said thiazole derivative and a salt thereof; a pharmaceutical composition comprising, as an active ingredient, said thiazole derivative or a pharmaceutically acceptable salt thereof; a use of said thiazole derivative or a pharmaceutically acceptable salt thereof as a medicament; and a method for using said thiazole derivative or a pharmaceutically acceptable salt thereof for therapeutic purposes, which comprises administering said thiazole derivative or a pharmaceutically acceptable salt thereof to a human being or an animal.

The thiazole derivatives of this invention are represented by the following formula (I):



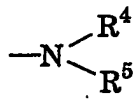
(I)

R is a 1-optionally substituted-6-oxo-1,6-dihydro-3-pyridazinyl,

R' is an optionally substituted phenyl,

R^2 is a hydrogen atom,

a group represented by the formula (i):



(i)

wherein

R^4 is hydrogen atom,

a lower alkyl group or

a lower alkenyl group, and

R^5 is hydrogen atom,

an optionally substituted lower alkyl group,

an acyl group,

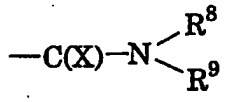
a cyclo(lower)alkyl group,

a lower alkenyl group,

an optionally substituted aryl group or

a heterocyclic group, or

a group represented by the formula (ii):



(ii)

wherein

X is an oxygen or sulfur atom,

R^8 is a hydrogen atom or

a lower alkyl group,

R^9 is a hydrogen atom,

an optionally substituted lower alkyl group,

a cyclo(lower)alkyl group,

a lower alkoxy group or

a mono- or di-lower alkylamino group or

R^8 and R^9 may combine together to form an optionally

substituted saturated N-containing heterocyclic group.

In the above and subsequent description of the present specification, suitable examples and illustrations of the various definitions, which the present invention includes within the scope, are explained in detail as follows.

The term "one or more" means 1 to 6, among which the preferred one is a number of 1 to 3, and the most preferred one is 1 or 2.

The term "lower" means a group having 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable examples of the lower alkyl group and the lower alky moieties in the mono- or di-lower alkylamino, halo(lower)alkyl, di(lower)alkylamino, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl, saturated or unsaturated heterocyclic(lower)alkyl, mono- or di-lower alkylamino(lower)alkyl, lower alkanoylamino(lower)alkyl, ar(lower)alkyl, ar(lower)alkylamino, pyrrolidon-1-yl(lower)alkyl, halo(lower)alkoxy, lower alkylsulfonyl, mono- or di-lower alkylcarbamoyl and ar(lower)alkylcarbamoyl groups are straight or branched ones having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, etc., in which the preferred one may be methyl, n-butyl, tert-butyl or hexyl.

Suitable examples of the halogen atom and halogen moieties in the halo(lower)alkyl and halo(lower)alkoxy groups are fluorine, chlorine, bromine or iodine.

Suitable examples of the lower alkenyl group are straight or branched ones having 1 to 6 carbon atom(s), such as ethenyl, 1- or 2-propenyl, butenyl, pentenyl, hexenyl, etc.

Suitable examples of the cyclo(lower)alkyl group and cyclo(lower)alkyl moiety in the cyclo(lower)alkylcarbonyl group are cyclo(C_3-C_8)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc., in which the preferred one may be cyclohexyl.

Suitable examples of the lower alkoxy group and the lower alkoxy moieties in the lower alkoxy(lower)alkyl, lower alkoxycarbonyl and lower alkoxy-substituted aryl groups are straight or branched ones having 1

to 6 carbon atoms such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-ethylbutoxy, isobutoxy, tert-butoxy, pentyloxy, n-hexyloxy, etc., in which the preferred one may be ones having 1 to 4 carbon atoms and the more preferred one may be methoxy.

Suitable examples of the acyl group include optionally substituted lower alkanoyl, cyclo(lower)alkylcarbonyl, lower alkoxycarbonyl, optionally substituted aroyl, aryloxycarbonyl, heterocyclic carbonyl, mono- or di-lower alkylcarbamoyl, ar(lower)alkylcarbamoyl, optionally substituted arylcarbamoyl and optionally substituted arylsulfonylcarbamoyl.

Suitable aryl and aryl moieties in the ar(lower)alkylamino, ar(lower)alkyl, aryloxy, arylamino, arylsulfonylamino, aroyl, aryloxycarbonyl, ar(lower)alkylcarbamoyl, arylcarbamoyl and arylsulfonylcarbamoyl groups are the ones having 6 to 18 carbon atoms such as phenyl, naphthyl, indenyl, anthryl, etc., in which the preferred one may be the one having 6 to 10 carbon atoms, and the more preferred one may be phenyl.

Suitable examples of the mono-lower alkylamino group are methylamino, ethylamino, propylamino and butylamino.

Suitable examples of the di-lower alkylamino group are dimethylamino, methyl(ethyl)amino, diethylamino, ethyl(propyl)amino and dipropylamino.

Suitable examples of the heterocyclic group and the heterocyclyl moieties in the saturated or unsaturated heterocyclic(lower)alkyl and heterocyclic carbonyl groups are saturated or unsaturated, monocyclic or condensed heterocyclic group containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur atoms.

Preferable examples of the heterocyclic group and the heterocyclyl moieties are described in the following.

(1) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl, pyrimidinyl, tetrahydropyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

(2) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidyl, piperidino, piperazinyl, etc.);

(3) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(4) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl, etc.);

(5) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), etc.;

(6) saturated 3 to 7-membered preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiomorpholinyl, thiazolidinyl, etc.);

(7) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms (e.g., furyl, pyranyl, etc);

(8) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms (e.g., 1,4-dioxanyl, etc);

(9) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms (e.g., thienyl, etc);

(10) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms (e.g., tetrahydrothienyl, etc);

(11) unsaturated condensed heterocyclic group containing 1 to 3 nitrogen atoms (e.g., benzopyrrolyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, quinolyl, isoquinolyl, indolyl, indolinyl, carbazolyl, 1,2,3,4-tetrahydroquinolyl, etc);

(12) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms (e.g., benzofuryl, benzodioxolyl, etc);

(13) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms (e.g., benzo[b]thienyl, etc.)

(14) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl, phenoxazinyl, etc); or

(15) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzisothiazolyl, phenothiazinyl, etc).

The N-containing heterocyclic group includes the ones described in (1), (2), (3), (4), (5), (6), (11), (14) and (15).

The saturated N-containing heterocyclic group includes the ones described in (2), (4) and (6).

Suitable examples of the substituent of the optionally substituted lower alkyl group are amino, imino, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, cyclo(lower)alkyl, aryl, optionally substituted, saturated or unsaturated heterocycle, carbamoyl, mono- or di-lower alkylamino and lower alkanoyl amino.

Suitable examples of the substituent of the optionally substituted aryl group are halo(lower)alkyl and di(lower)alkylamino.

Suitable examples of the substituent of the optionally substituted saturated N-containing heterocyclic group are lower alkyl, lower alkanoyl, aryl and ar(lower)alkyl.

Suitable examples of the substituent of the optionally substituted aroyl group are halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy and a group represented by the formula : $-CH_2-NR^{12}R^{13}$ wherein R^{12} and R^{13} are defined in the below.

Suitable examples of the substituent of the optionally substituted arylcarbamoyl group are lower alkyl, etc.

Suitable examples of the substituent of the optionally substituted arylsulfonylcarbamoyl group are lower alkyl, etc.

Suitable examples of the lower alkanoyl group and lower alkanoyl moieties in the lower alkanoylamino and lower

alkanoylamino(lower)alkyl groups are formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc., in which the preferred one may be (C_1-C_4)alkanoyl and the more preferred one may be acetyl.

Suitable examples of halo(lower)alkyl group are C_{1-4}, preferably C_{1-2} alkyl group containing 1 to 9, preferably 1 to 5 halogen atoms, preferably fluorine, chlorine and/or bromine atom(s), more preferably fluorine and/or chlorine atom(s). Preferable examples the halo(lower)alkyl group are chloromethyl, bromomethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, trifluoromethyl, trichloromethyl, chlorodifluoromethyl, dichlorofluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl.

Suitable examples of halo(lower)alkoxy group are C_{1-4}, preferably C_{1-2} alkoxy group containing 1 to 9, preferably 1 to 5 halogen atoms, preferably fluorine, chlorine and/or bromine atom(s), more preferably fluorine and/or chlorine atom(s). Preferable examples are chloromethoxy, bromomethoxy, 1-fluoroethoxy, 2-fluoroethoxy, trifluoromethoxy, trichloromethoxy, chlorodifluoromethoxy, dichlorofluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy and pentafluoroethoxy.

Suitable examples of the ar(lower)alkyl group and ar(lower)alkyl moieties in the ar(lower)alkylamino and ar(lower)alkylcarbamoyl groups are benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, benzhydryl, trityl and naphthylmethyl.

Suitable examples of the lower alkoxy-substituted aryl are 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 2-, 3- or 4-propoxyphenyl, 2-, 3- or 4-methoxynaphthyl and 2-, 3- or 4-ethoxynaphthyl.

Suitable examples of the hydroxy(lower)alkyl group are hydroxymethyl, 1- or 2-hydroxyethyl, 1,2-dihydroxyethyl, 1-, 2- or 3-propyl, 1,2-, 2,3- or 1,3-dihydroxypropyl, 1-, 2-, 3- or 4-hydroxybutyl and 1,2-, 2,3-, 3,4-, 1.3-, 1,4- or 2,4-dihydroxybutyl.

Suitable examples of the lower alkoxy(lower)alkyl group are methoxymethyl, 1- or 2-methoxyethyl, 1- or 2-ethoxyethyl, 1-, 2- ot 3-methoxypropyl and 1-, 2- or 3-ethoxypropyl.

Suitable examples of the saturated or unsaturated heterocyclic(lower)alkyl group are piperidylmethyl, 1- or 2-piperidylethyl, morpholinylmethyl, 1- or 2-morpholinylethyl, 1-, 2- or 3-morpholinylpropyl, pyridylmethyl, and 1- or 2-pyridylethyl,

Suitable examples of the mono- or di-lower alkylamino(lower)alkyl group are methylaminomethyl, dimethylaminomethyl, 1- or 2-methylaminoethyl, 1- or 2-dimethylaminoethyl, 1- or 2-ethylaminoethyl, 1- or 2-diethylaminoethyl, 1-, 2- or 3-methylaminopropyl and 1-, 2- or 3-dimethylaminopropyl.

Suitable examples of the lower alkanoylamino(lower)alkyl group are acetylaminomethyl, 1- or 2-acetylaminoethyl, propionylaminomethyl and 1- or 2-butyrylaminoethyl.

Suitable examples of the hydroxy- or sulfamoyl-substituted ar(lower)alkyl group are 2-, 3- or 4-hydroxyphenylmethyl, 2-, 3- or 4-sulfamoylphenylmethyl, 2-, 3- or 4-hydroxyphenylethyl, 2-, 3- or 4-sulfamoylphenylethyl, 2-hydroxy-2-phenylethyl and 1-hydroxy-2-phenylethyl.

Suitable examples of the lower alkyl-substituted, saturated or unsaturated heterocyclic group are 3-, 4-, 5- or 6-methylpyrid-2-yl, 3-, 5- or 6-methylpyrazin-2-yl and 2- or 3-methylpyrid-4-yl.

It is to be noted that the object compound (I) may include stereo isomer(s) due to the asymmetric carbon atom(s).

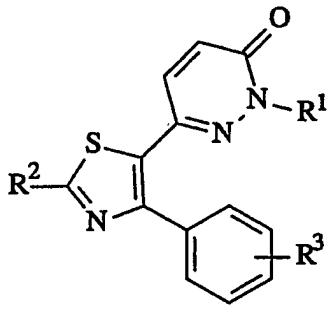
Suitable salts of the object compound (I) are conventional pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic

acid, etc.), etc.

The compound of the formula (I) and its salt can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

Preferred embodiments of the object compounds (I) are the one represented by the formula (I-1):



(I-1)

wherein

R^1 is a hydrogen atom,

an optionally substituted lower alkyl group,

a lower alkenyl group, or

a cyclo(lower)alkyl,

R^2 is as defined in the above, and

R^3 is a hydrogen atom, a halogen atom, a hydroxy group, a lower alkyl group or a lower alkoxy group.

More preferred embodiments of the object compounds (I-1) are the one wherein

R^1 is a hydrogen atom;

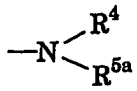
a lower alkyl group which may be substituted with lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, cyclo(lower)alkyl or aryl;

a lower alkenyl group; or

a cyclo(lower)alkyl;

R^2 is a hydrogen atom,

a group represented by the formula (ia):



(ia)

wherein

R^4 is a hydrogen atom,

a lower alkyl group or

a lower alkenyl group, and

R^{5a} is a hydrogen atom;

a lower alkyl group which may be substituted with one or more substituents selected from amino, imino, lower alkoxy, aryl and saturated or unsaturated heterocyclic group;

a lower alkyl sulfonyl group;

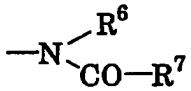
a cyclo(lower)alkyl group;

a lower alkenyl group;

an aryl group which may be substituted with halo(lower)alkyl or di(lower)alkylamino;

an unsaturated heterocyclic group,

a group represented by the formula (iii):



(iii)

wherein

R^6 is a hydrogen atom or

a lower alkyl group,

and

R^7 is a hydrogen atom;

a cyclo(lower)alkyl group;

a lower alkoxy group;

an aryloxy group;

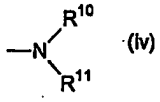
a saturated or unsaturated heterocyclic group;

a mono- or di-lower alkylamino group;

an ar(lower)alkylamino group;

a lower alkyl group which may be substituted with halogen, aryl, lower alkoxy-substituted aryl, aryloxy,

or a group of the formula (iv):



(iv)

wherein

R^{10} is a hydrogen atom or a lower alkyl group,

R^{11} is a lower alkyl group, a cyclo(lower)alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a saturated or unsaturated heterocyclic(lower)alkyl group, a mono- or di-lower alkylamino(lower)alkyl group, a lower alkanoylamino(lower)alkyl group, an ar(lower)alkyl group, a hydroxy- or sulfamoyl-substituted ar(lower)alkyl group or a pyrrolidonyl(lower)alkyl group,

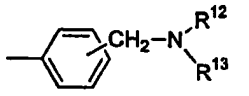
or R^{10} and R^{11} may combine together to form a N-containing heterocyclic group which may be substituted with lower alkyl or lower alkanoyl;

an arylamino group which may be substituted with lower alkyl;

an arylsulfonylamino group which may be substituted with lower alkyl; or

an aryl group which may be substituted with one or more of substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy, and

a group of the formula (v):



(v)

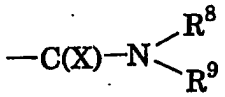
wherein

R^{12} is a hydrogen atom or a lower alkyl group,

R^{13} is a lower alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a saturated or unsaturated heterocyclic(lower)alkyl group, or a mono- or di-lower alkylamino(lower)alkyl group,

or R^{12} and R^{13} may combine together to form a N-containing heterocyclic group which may be substituted with lower alkyl, and

a group represented by the formula (ii):



(ii)

wherein

X is an oxygen or sulfur atom,

R^8 is a hydrogen atom or

a lower alkyl group,

R^9 is a hydrogen atom;

a lower alkyl group which may be substituted with carbamoyl, lower alkoxy, mono- or di-lower alkylamino, lower alkanoylamino, aryl, or unsubstituted or lower alkyl-substituted, saturated or unsaturated heterocyclic group;

a cyclo(lower)alkyl group;

a lower alkoxy group; or

a mono- or di-lower alkylamino group; or

R^8 and R^9 may combine together to form a saturated N-containing heterocyclic group which may be substituted with lower alkyl, lower alkanoyl, aryl or ar(lower)alkyl;

and

R^3 is a hydrogen atom, a halogen atom, a hydroxy group, a lower alkyl group or a lower alkoxy group.

Further preferred embodiments of the object compounds (I-1) are the one wherein

R^1 is a hydrogen atom;

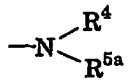
a lower alkyl group which may be substituted with lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, cyclo(lower)alkyl or phenyl;

a lower alkenyl group; or

a cyclo(lower)alkyl;

R^2 is a hydrogen atom,

a group represented by the formula (ia):



(ia)

wherein

R^4 is a hydrogen atom,

a lower alkyl group or

a lower alkenyl group, and

R^{5a} is a hydrogen atom;

a lower alkyl group which may be substituted with one or more substituents selected from amino, imino, lower alkoxy, phenyl, piperidyl, morpholinyl, pyridyl or furyl;

a lower alkyl sulfonyl group;

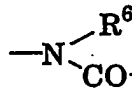
a cyclo(lower)alkyl group;

a lower alkenyl group;

a phenyl or naphthyl group which may be substituted with halo(lower)alkyl or di(lower)alkylamino;

a pyridyl group,

a group represented by the formula (iii):



(iii)

wherein

R^6 is a hydrogen atom or

a lower alkyl group,

and

R^7 is a hydrogen atom;

a cyclo(lower)alkyl group;

a lower alkoxy group;

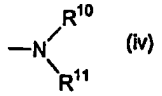
a phenoxy group;

a piperidyl, morpholinyl, pyridyl or carbazolyl group;

a mono- or di-lower alkylamino group;

a phenyl(lower)alkylamino group;

a lower alkyl group which may be substituted with halogen, phenyl, lower alkoxy-substituted phenyl, phenoxy, or a group of the formula (iv):



(iv)

wherein

R^{10} is a hydrogen atom or a lower alkyl group,

R^{11} is a lower alkyl group, a cyclo(lower)alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a piperidyl(lower)alkyl, a morpholinyl(lower)alkyl or a pyridyl(lower)alkyl group, a mono- or di-lower alkylamino(lower)alkyl group, a lower alkanoylamino(lower)alkyl group, a phenyl(lower)alkyl group, a hydroxy- or sulfamoyl-substituted phenyl(lower)alkyl group or a pyrrolidonyl(lower)alkyl group,

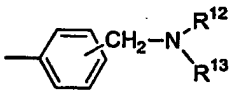
or R^{10} and R^{11} may combine together to form a imidazolyl, pyrrolidinyl, piperidyl, morpholinyl or piperazinyl group which may be substituted with lower alkyl or lower alkanoyl;

an phenylamino group which may be substituted with lower alkyl;

an phenylsulfonylamino group which may be substituted with lower alkyl; or

a phenyl or naphthyl group which may be substituted with one or more of substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy, and

a group of the formula (v):



(v)

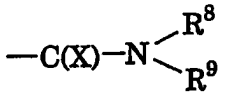
wherein

R^{12} is a hydrogen atom or a lower alkyl group,

R^{13} is a lower alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a piperidyl(lower)alkyl, a morpholinyl(lower)alkyl or a

pyridyl(lower)alkyl group, or a mono- or di-lower alkylamino(lower)alkyl group,
or R^{12} and R^{13} may combine together to form a imidazolyl, pyrrolidinyl, piperidyl, morpholinyl or piperazinyl group which may be substituted with lower alkyl, and

a group represented by the formula (ii):



(ii)

wherein

X is an oxygen or sulfur atom,

R^8 is a hydrogen atom or
a lower alkyl group,

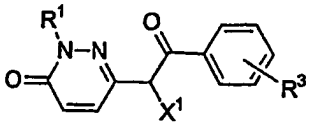
R^9 is a hydrogen atom;
a lower alkyl group which may be substituted with carbamoyl, lower alkoxy, mono- or di-lower alkylamino, lower alkanoylamino, phenyl, morpholinyl, pyridyl or pyrazinyl which may be substituted with lower alkyl;
a cyclo(lower)alkyl group;
a lower alkoxy group; or
a mono- or di-lower alkylamino group; or

R^8 and R^9 may combine together to form a pyrrolidinyl, piperidyl, morpholinyl or piperazinyl group which may be substituted with lower alkyl, lower alkanoyl, phenyl or phenyl(lower)alkyl and

R^3 is a hydrogen atom, a halogen atom, a hydroxy group, a lower alkyl group or a lower alkoxy group.

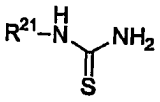
The object compounds (I) and (I-1) and a salt thereof of the present invention can be prepared by the following processes.

Process 1

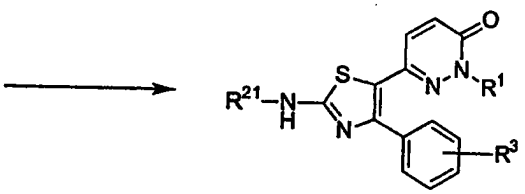


(II)
or a salt thereof

+

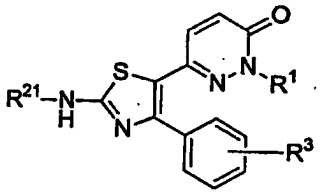


(III)
or a salt thereof



(I-1a)
or a salt thereof

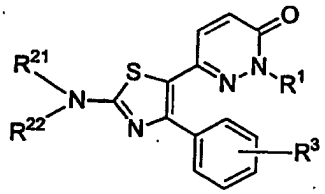
Process 2



(I-1a)
or a salt thereof

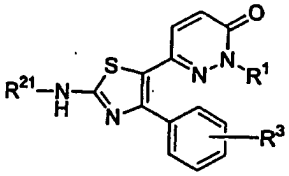
+ R^{22}—Y

(IV)



(I-1b)
or a salt thereof

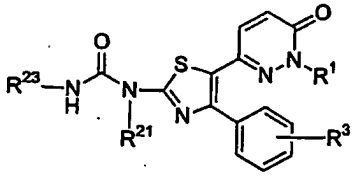
Process 3



(I-1a)
or a salt thereof

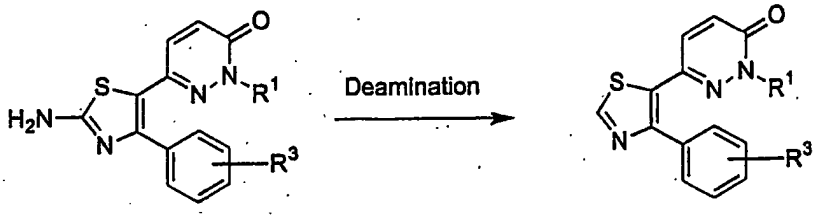
+ R^{23}—NCO

(V)
or a salt thereof



(I-1c)
or a salt thereof

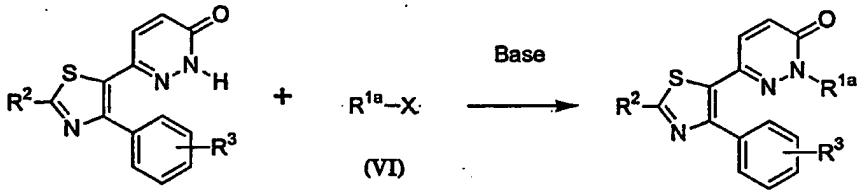
Process 4



(I-1d)
or a salt thereof

(I-1e)
or a salt thereof

Process 5

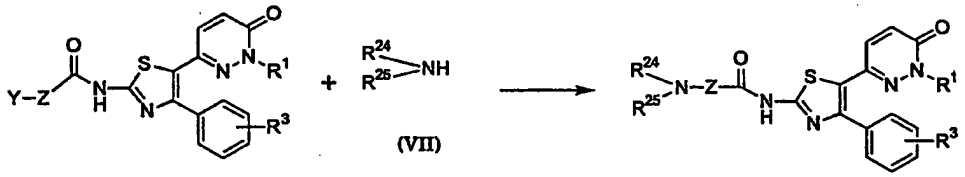


(I-1f)
or a salt thereof

(VI)

(I-1g)
or a salt thereof

Process 6

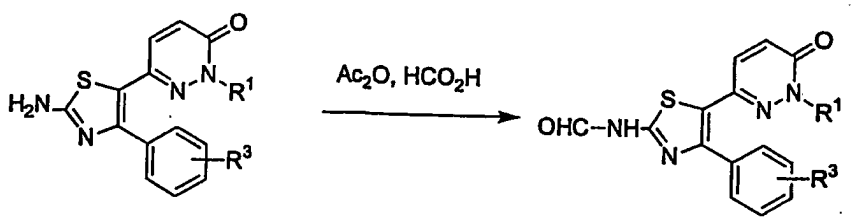


(I-1h)
or a salt thereof

(VII)

(I-1j)
or a salt thereof

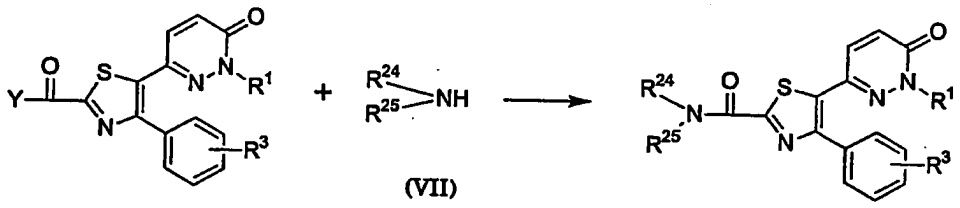
Process 7



(I-1d)
or a salt thereof

(I-1k)
or a salt thereof

Process 8

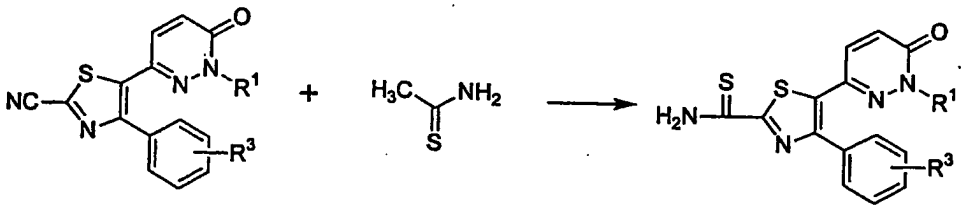


(VIII)
or a salt thereof

(VII)

(I-1m)
or a salt thereof

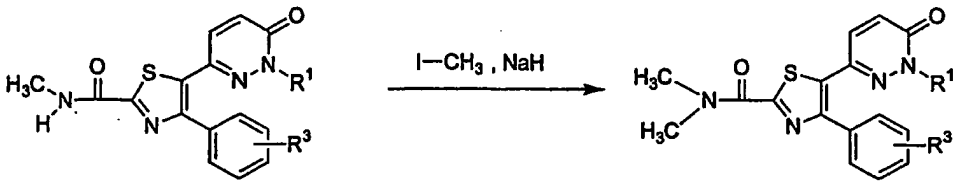
Process 9



(IX)
or a salt thereof

(I-1n)
or a salt thereof

Process 10



(I-1o)
or a salt thereof

(I-1p)
or a salt thereof

wherein

R^1, R^2 and R^3 are as defined above,

R^{1a} is an optionally substituted lower alkyl, lower alkenyl or cyclo(lower)alkyl group,

R^{21} is a hydrogen atom or an optionally substituted lower alkyl, optionally substituted aryl, cyclo(lower)alkyl, heterocycle or acyl group,

R^{22} is an optionally substituted lower alkyl, acyl or lower alkenyl group,

R^{23} is a hydrogen atom, an optionally substituted aryl, optionally substituted lower alkyl, acyl or heterocyclic group,

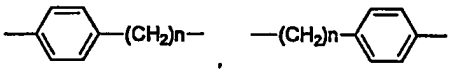
R^{24} is a hydrogen atom or a lower alkyl group,

R^{25} is an optionally substitutted lower alkyl, cyclo(lower)alkyl, pyrrolidonyl(lower)alkyl, optionally substituted lower alkanoyl, or di-lower alkylamino group, or

R^{24} and R^{25} may combine together to form an optionally substituted heterocyclic group,

X^1 is a halogen atom,

Y is a leaving group.

Z is $-(CH_2)_n-$,  or phenylene, and

n is 1 or 2.

Suitable leaving group are halogen as mentioned above, hydroxy, acyloxy such as alkanoyloxy (e.g. acetoxy, propionyloxy, etc.), lower alkoxy (e.g., ethoxy etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.), etc.

Suitable salt of the compounds (I-1a), (I-1b), (I-1c), (I-1d), (I-1e), (I-1f), (I-1g), (I-1h), (I-1j), (I-1k), (I-1m), (I-1n), (I-1o), (I-1p), (II), (III), (V), (VIII) and (IX) can be referred to the ones as examplified for the compound (I).

The processes for preparing the object thiazole derivative(I) are explained in detail in the following.

Process 1

The compound (I-1a) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the thiourea derivative (III) or a salt thereof.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine, etc.

The reaction may be carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction. These conventional solvents may also be used in a mixture with water.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 2

The compound (I-1b) or a salt thereof can be prepared by reacting the compound (I-1a) or a salt thereof with a compound (IV).

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium

hydroxide, potassium hydroxide, etc.), alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. triethylamine, etc.), etc.

Alternatively, the present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) etc.

When Y is –OH, activation of OH with triphenylphosphine and the like may be necessary.

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, pyridine or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (IV) is in liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 3

The compound (I-1c) or a salt thereof can be prepared by reacting the compound (I-1a) or a salt thereof with the compound (V) or a salt thereof.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. triethylamine, etc.), etc.

Alternatively, the present reaction is preferably carried out in the

presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) etc.

The present reaction may be carried out in a solvent such as acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, pyridine or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. When the compound (V) is in liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 4

The compound (I-1e) or a salt thereof can be prepared by subjecting the compound (I-1d) or a salt thereof to deamination reaction.

The deamination reaction can be carried out in the presence of isoamyl nitrate in a solvent such as chloroform, acetonitrile, methylene chloride, diethyl ether, dioxane, tetrahydrofuran or any other organic solvent which does not adversely affect the reaction. The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 5

The compound (I-1g) or a salt thereof can be prepared by reacting the compound (I-1f) or a salt thereof with a compound (VI).

The reaction is usually conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal

alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g., triethylamine), and the like.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 6

The compound (I-1j) or a salt thereof can be prepared by reacting the compound (I-1h) or a salt thereof with amine derivative (VII).

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine, and the like.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 7

The compound (I-1k) or a salt thereof can be prepared by reacting the compound (I-1d) or a salt thereof with acetic anhydride and formic acid.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 8

The compound (I-1m) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the amine (VII).

The reaction of this process can be carried out in the manner similar to that of Process 6.

Process 9

The compound (I-1n) or a salt thereof can be prepared by reacting the compound (IX) or a salt thereof with thioacetamide.

The reaction is preferably conducted in the presence of an acid, for example, organic acid such as acetic acid or inorganic acid such as hydrochloric acid, hydrobromic acid, etc.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

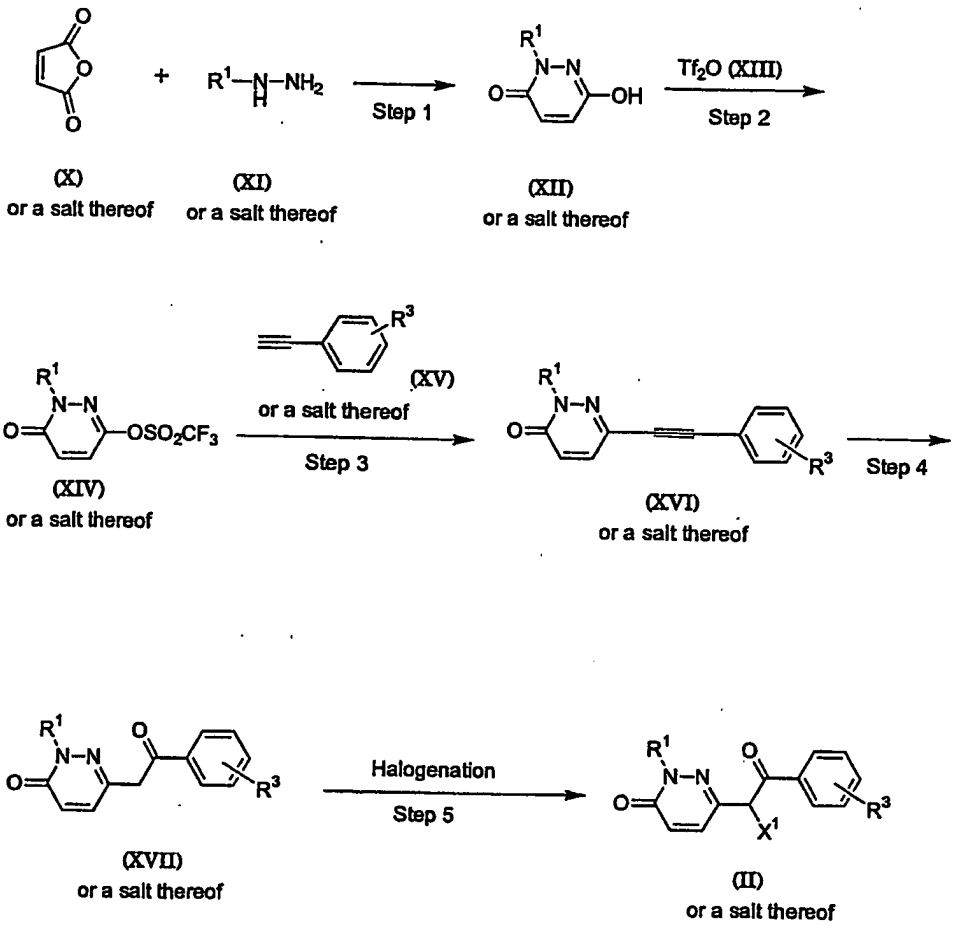
Process 10

The compound (I-1p) or a salt thereof can be prepared by reacting the compound (I-1o) or a salt thereof with methyl idodide and base.

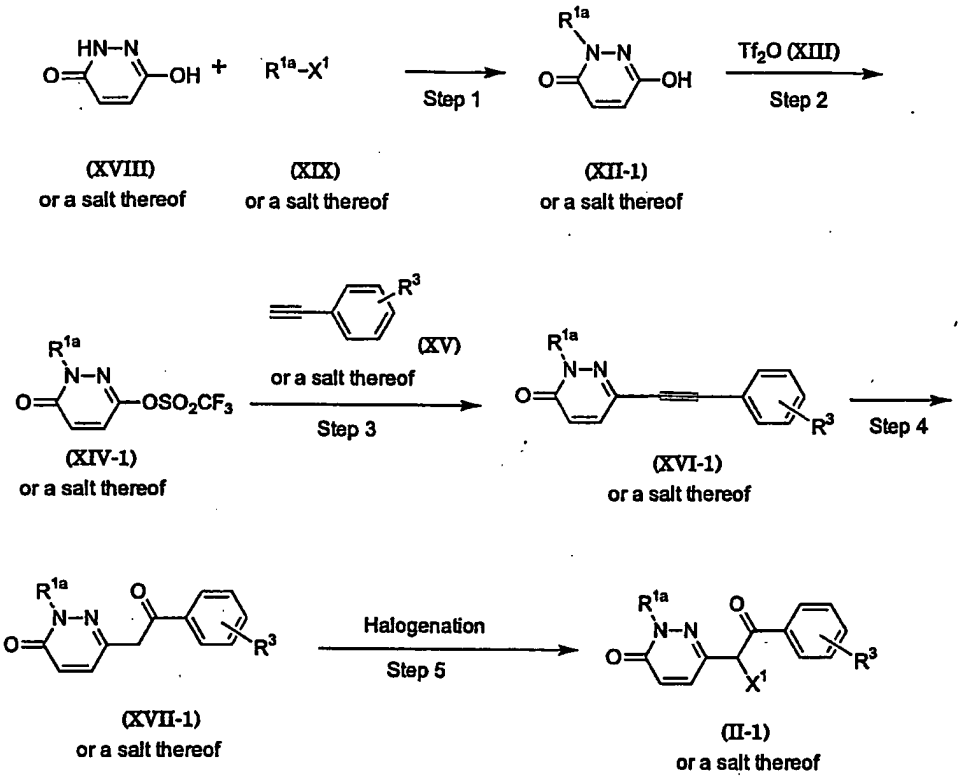
The reaction of this process can be carried out in the manner similar to that of Process 5.

The starting compounds (II), (II-1), (VIII), (VIII-2) and (IX) or a salt thereof are novel and can be prepared, for example, by the following reaction schemes.

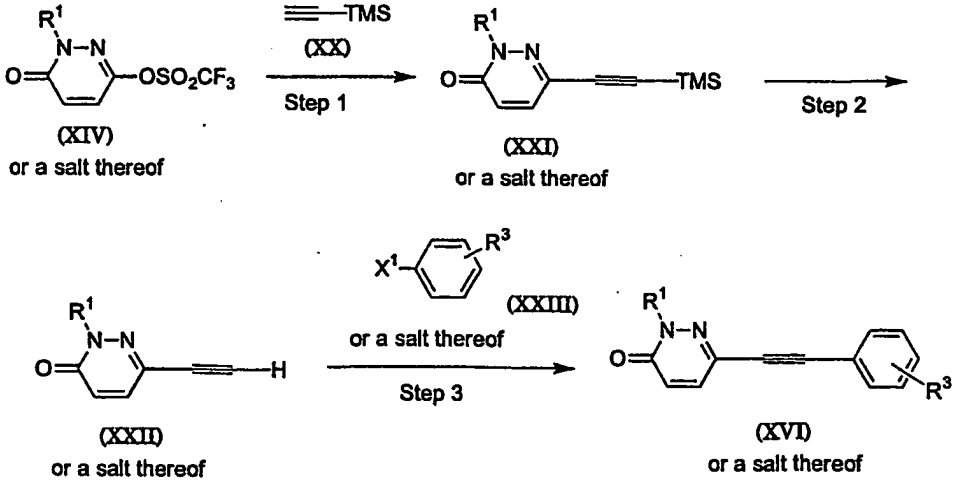
Process A



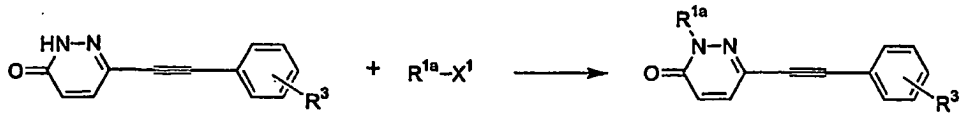
Process B



Process C

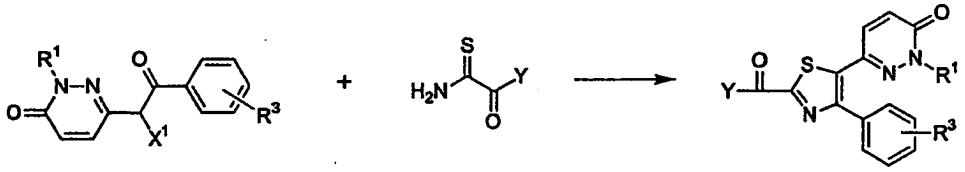


Process D



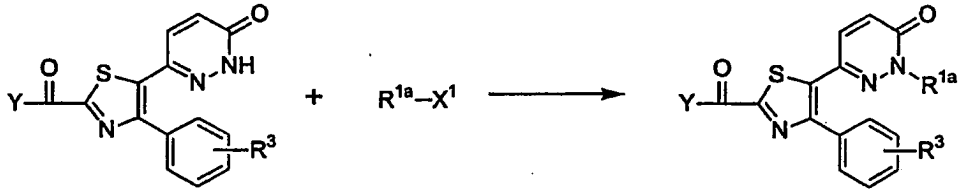
(XVI-2) or a salt thereof + (XIX) or a salt thereof → (XVI-1) or a salt thereof

Process E



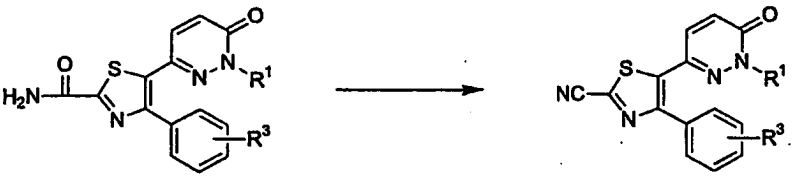
(II) or a salt thereof + (XXIV) or a salt thereof → (VIII) or a salt thereof

Process F



(VIII-1) or a salt thereof + (XIX) or a salt thereof → (VIII-2) or a salt thereof

Process G



(XXV) or a salt thereof → (IX) or a salt thereof

wherein R^1, R^3, Y, R^{1a} and X^1 are as defined above,

Tf_2O is trifluoromethanesulfonic anhydride,

TMS is trimethylsilyl and

Steps 2 to 5 of Process B are as same as those of Process A.

Suitable salt of the compounds (II), (II-1), (VIII), (VIII-1), (VIII-2), (IX), (X), (XI), (XII), (XII-1), (XIV), (XIV-1), (XV), (XVI), (XVI-1), (XVI-2), (XVII), (XVII-1), (XVIII), (XIX), (XXI), (XXII), (XXIII), (XXIV) and (XXV) can be referred to the ones as examplified for the compound (I).

Process A

Step 1: The compound (XII) or a salt thereof can be prepared by reacting the compound (X) or a salt thereof and the compound (XI) or a salt thereof. The reaction is usually carried out in the presence of an acid, for example, organic acid such as acetic acid or inorganic acid such as hydrochloric acid, hydrobromic acid, etc.

This reaction is usually carried out in a conventional solvent such as alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction. The acid can be used as the solvent if it is liquid.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating, preferebly under heating.

Step 2: The compound (XIV) or a salt thereof can be prepared by reacting the compound (XII) or a salt thereof with trifluoromethane sulfonic acid anhydride (XIII). The reaction is usually carried out in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine, pyridine and the like.

The reaction may be carried out in a conventional solvent such as dioxane, acetonitrile, chloroform, methylene chloride, ethylene

chloride, tetrahydrofuran, ethyl acetate, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating, preferebly under heating.

Step 3: The compound (XVI) or a salt thereof can be prepared bycoupling the compound (XIV) or a salt thereof and the compound (XV) or a salt thereof.

The reaction is usually conducted in the presence of palladium and copper catalyst such as dichlorobis(triphenylphosphine)palladium (II) and copper (I) iodide.

Besides, the reaction is usually carried out in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine, pyridine and the like.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Step 4: The compound (XVII) or a salt thereof can be prepared by reacting the compound (XVI) or a salt thereof with sulfuric acid and acetic acid.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide,

pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Step 5: The compound (II) or a salt thereof can be prepared by subjecting the compound (XVII) or a salt thereof to halogenation. Halogenation reaction can be carried out in the presence of pyridinium tribromide or sulfuryl chloride.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, acetic acid or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process B

The compound (II-1) or a salt thereof can be prepared by reacting the compound (XVIII) or a salt thereof with the compound (XIX) by Steps 1 to 5.

Step 1: The compound (XII-1) or a salt thereof can be prepared by reacting the compound (XVIII) or a salt thereof with a silylation reagent and then reacting with a halide compound (XIX) or a salt thereof.

The silylation usually proceeds in the presence of a silylating reagent such as N, N'-bis(trimethylsilyl)urea (BSU), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), etc. and optionally a catalyst such as sulfuric acid. The amount of the silylating reagent is preferably more than 2 equivalent of the compound (XVIII) or a salt thereof. The silylation may be carried out in a conventional solvent such as dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, benzene, toluene or any other organic solvent which

does not adversely affect the reaction.

The reaction temperature of the silylation is not critical, and the reaction is preferably carried out under heating.

After silylation, both the silylating reagent and the solvent are preferably removed such as evaporation. Then, the silylated compound can be reacted with the halide compound (XIX) or a salt thereof in a solvent such as the one having the high inductivity, for example o-dichlorobenzene, nitrobenzene, ethylene carbonate, propylene carbonate, etc. The amount of the halide compound (XIX) is at least 1 equivalent, preferably more than 1 equivalent of the compound (XVIII).

The reaction temperature is not critical, and the reaction is preferably carried out under heating.

Silylation of 3,6-dihydroxypyridazine improves its reactivity and solubility and using the solvent having the high inductivity for the alkylation with the compound (XIX) can facilitate preparing the compound (XII-1).

The Steps 2 to 5 can be respectively carried out in a manner similar to Steps 2 to 5 of Process A.

Process C

Step 1: The compound (XVI) or a salt thereof can be prepared by reacting the compound (XIV) or a salt with the compound (XX). The Step 1 can be carried out in a manner similar to Step 3 of Process A.

Step 2: The compound (XXII) or a salt thereof can be prepared by subjecting the compound (XXI) or a salt thereof to a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate(e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate(e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g.

EtONa, t-BuOK, etc.) organic base such as trialkylamine, pyridine and the like.

The reaction may be carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction. These conventional solvents may also be used in a mixture with water.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Step 3: The Step 3 can be carried out in a manner similar to Step 3 of Process A.

Process D

The compound (XVI-1) or a salt thereof can be prepared by reacting the compound (XVI-2) or a salt thereof with the compound (XIX) or a salt thereof.

The reaction of this process can be carried out in a manner similar to Process 5.

Process E

The compound (VIII) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (XXIV) or a salt thereof.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process F

The compound (VIII-2) or a salt thereof can be prepared by reacting the compound (VIII-1) or a salt thereof with the compound (XIX) or a salt thereof.

The reaction of this process can be carried out in a manner similar to Process 5.

Process G

The compound (IX) or a salt thereof can be prepared by reacting the compound (XXV) or a salt thereof with trifluoroacetic anhydride and pyridine.

The reaction may be carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

In order to show the usefulness of the compound (I) of the present invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1 : Adenosine antagonistic activity

[I] Test method

The adenosine antagonistic activity [Ki(nM)] of the test compound was examined by radioligand binding techniques using 8-cyclopentyl-1,3-dipropylxanthine, [dipropyl-2,3-^{3}H(N)] ([^{3}H]DPCPX, 4.5nM) for human A_1 receptor and [^{3}H]CGS 21680 (20nM) for human A_{2a} receptor.

[II] Test compound

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4- phenyl-1,3-thiazol-2-yl]hexanamide (Example 3)

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)–4- phenyl-1,3-thiazol-2-yl]-2-(4-methoxy-phenyl)acetamide (Example 9)

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4- phenyl-1,3-thiazol-2-yl]-N'-(3-methylphenyl)urea (Example 10)

2-Isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol- 5-yl]-3(2H)-pyridazinone (Example 15)

[III] Test result

Table 1

Test compound (Example No.)	Adenosine receptor binding (Ki: nM)	
	A_1	A_{2a}
3	0.27	1.46
9	0.28	1.22
10	0.38	3.08
15	0.12	1.63
78	0.45	1.23
100	0.61	1.22
214	1.14	1.52
233	1.03	1.14

Test 2 : Anticatalepsy activity in Mouse

[I] Test method

The test compound (3.2mg/kg) was administered orally with ddY mice(n=7). Then, haloperidol (0.32mg/kg) was injected intraperitoneally 30 min. after the administration of the compound. Thirty minutes after the injection, the cataleptic responses of mice were measured. The forelimbs of each mouse were placed on a 3 cm high, 3 mm wide horizontal bar, and the duration of cataleptic posture was measured for up to 30 sec.

[II] Test compound

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4- phenyl-1,3-

thiazol-2-yl]hexanamide (Example 3)

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4- phenyl-1,3-thiazol-2-yl]-2-(4-methoxyphenyl)acetamide (Example 9)

2-Isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol- 5-yl]-3(2H)-pyridazinone (Example 15)

[III] Test result

Table 2

Test compound (Example No.)	Manifestation rate of catalepsy (number of mouse)
3	0/7
9	0/7
15	0/7
78	0/7
100	0/7
214	0/7
233	0/7

The thiazole derivatives of the present invention have an adenosine antagonistic activity and pharmacological action such as anticatalepsy activity as shown in the above.

The thiazole derivative and a salt thereof of the present invention are useful as adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and possess various pharmacological actions such as anticatalepsy action, cognitive enhancing action, analgesic action, locomotor action, antidepressant action, diuretic action, cardioprotective action, cardiotonic action, vasodilating action (e.g. cerebral vasodilating action, etc.), the action of increasing the renal blood flow, renal protective action, improvement action of renal function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin release, the action of increasing the production of erythropoietin, inhibiting action of platelet aggregation, etc.

Therefore, the thiazole derivative (I) and a salt thereof of this

invention are useful as cognitive enhancer, antianxietry drug, antidementia drug, psychostimulant, analgesic, cardioprotective agent, antidepressant, ameliorants of cerebral circulation, tranquilizer, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal failure (renal insufficiency), drug for renal toxicity, renal protective agent, drug for improvement of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilator, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppressive action of adenosine, antidiabetic agent, drug for ulcer, drug for pancreatitis, drug for Meniere's syndrome, drug for anemia;
drug for thrombosis, drug for myocardial infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, drug for angina pectoris, etc.;
and useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure; hypertension (e.g. essential hypertension, nephrogenous hypertension, etc.);
circulatory insufficiency (acute circulatory insufficiency) cuased by, for example, ischemia/reperfusion injury (e.g. myocardial ischemia/reperfusion injury, cerebral ischemia/reperfusion injury, peripheral ischemia/reperfusion injury, etc.), shock (e.g. endotoxin shock, hemorrhagic shock, etc.), surgical procedure, etc.;
post-resuscitation asystole;
bradyarrhythmia;
electro-mechanical dissociation;
hemodynamic collapse;
SIRS (systemic inflammatory response syndrome);
multiple organ failure;
renal failure (renal insufficiency) (e.g. acute renal failure, etc.), renal toxicity [e.g. renal toxicity induced by a drug such as cisplatins, gentamicin, FR-900506 (disclosed in EP-0184162), cyclosporin (e.g.

cyclosporin A) etc.; glycerol, etc.], nephrosis, nephritis, edema (e.g. cardiac edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, carcinomatous ascites, gestational edema, etc.);

obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer such as peptic ulcer (e.g. gastric ulcer, duodenal ulcer, etc.), pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus (e.g. mechanical ileus, adynamic ileus, etc.); and

myocardial infarction, thrombosis (e.g. arterial thrombosis, cerebral thrombosis, etc.), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, etc.

The present invention provides a pharmaceutical composition which contains the thiazole derivative (I) or a pharmaceutically acceptable salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The pharmaceutical composition of this invention can be formulated in the form of a pharmaceutical preparation, for example, in a solid, semisolid or liquid form. The examples of the carrier or excipient are non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. In addition, auxiliary, stabilizing agents, thickening agents, coloring agents and perfumes may be used where it is necessary. The thiazole derivative (I) or a pharmaceutically acceptable salt thereof is included in a pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous, intramuscular, pulmonary or oral

administration, or insufflation. While the dosage of therapeutically effective amount of the thiazole derivative (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the thiazole derivative (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.1 - 100 mg of the thiazole derivative (I) per kg weight of a human being or an animal, and in case of oral administration, a daily dose of 0.5 - 100 mg of the thiazole derivative (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the aforesaid diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of maleic anhydride (41.57 g) in glacial acetic acid (310 ml) was added 1-isopropyl-hydrazine (31.43 g) at ambient temperature. The mixture was heated under reflux for 5 hours and then concentrated under reduced pressure to give a solid. The solid was triturated by diisopropyl ether, collected by filtration and recrystalized from a mixture of methanol and isopropyl ether to give 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (60.27 g).
mp: 162-164°C
IR(KBr): 1504 cm^{-1}
^1H NMR($CDCl_3$,δ): 1.22(6H,d,J=6.66 Hz), 5.03(1H,7-plet,J=6.65 Hz), 6.85(1H,d,J=9.62 Hz), 7.01(1H,d,J=9.62 Hz), 10.95(1H,br.s)
APCI/MS: 155$[M+H]^+$
Elemental Analysis for $C_7H_{10}N_2O_2$
Calcd.: C,54.54; H,6.54; N,18.17
Found : C,54.72; H,6.61; N,18.13

Preparation 2

To a solution of 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (5.00 g)

in pyridine (32 ml) was dropwise added tifluoromethanesulfonic anhydride (5.51 ml) under ice-cooling. The mixture was stirred for one hour under ice-cooling and for 3 hours at ambient temperature. Pyridine was removed under reduced pressure to give a residue. The residue was dissolved in a mixture of ethyl acetate and water. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 8:2 ,v/v) to give 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate as a solid (8.66 g).
mp: 45-46°C
IR(KBr): 1660, 1587 cm^{-1}
^1H NMR($CDCl_3$,δ): 1.34(6H,d,J=6.62 Hz), 5.23(1H,7-plet,J=6.61 Hz), 7.04(1H,d,J=9.83Hz), 7.16(1H,d,J=9.83Hz)
APCI/MS: 287$[M+H]^+$
Elemental Analysis for $C_8H_9F_3N_2O_4S$
Calcd.: C,33.57; H,3.17; N,9.79
Found : C,33.80; H,2.96; N,9.79

Preparation 3

In the presence of dichlorobis(triphenylphosphine)palladium (II)(0.49 g) and copper(I)iodide (0.133 g), a solution of triethylamine (11.7 ml) in dioxane (10 ml) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (20.00 g), ethynylbenzene (8.56 g) in dioxane (70 ml) at 75-80°C for 0.5 hour. The mixture was stirred for 1.5 hours at 75-80°C. After cooling, a mixture of water and chloroform was added to the mixture. The separated organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 85:15, v/v) to give 2-isopropyl-6-(phenylethynyl)-3(2H)- pyridazinone as a solid (16.17 g).
mp: 75.5-77°C
IR(KBr): 2218, 1669, 1583 cm^{-1}

^{1}H NMR($CDCl_3$,δ): 1.40(6H,d,J=6.65Hz), 5.33(1H,7-plet,J=6.65Hz), 6.87(1H,d,J=9.57Hz), 5.13(1H,d,J=9.57Hz), 7.34-7.42(3H,m), 7.52-7.60(2H,m)

APCI/MS: 239$[M+H]^+$, 197

Elemental Analysis for $C_{15}H_{14}N_2O$

Calcd.: C,75.61; H,5.92; N,11.76

Found : C,75.79; H,5.88; N,11.74

Preparation 4

To a mixture of sulfuric acid (1 ml) and acetic acid (3 ml) was added 2-isopropyl-6-(phenyl-ethynyl)-3(2H)-pyridazinone (479 mg), and the mixrture was heated for 2 hours at 100-105°C. The solution was poured into ice-water (80 ml) and extracted with ethyl acetate (30 ml x 3). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 1:3, v/v) to give 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone as a solid (451 mg).

mp: 50-53°C

IR(KBr): 1687, 1660, 1595 cm^{-1}

^{1}H NMR($CDCl_3$,δ): 1.32(6H,d,J=6.66Hz), 4.32(2H,s), 5.29(1H,7-plet, J=6.66Hz), 6.88(1H,d,J=9.50Hz), 7.18(1H,d,J=9.50Hz), 7.45-7.62(3H,m), 8.01-8.07(2H,m)

APCI/MS: 257$[M+H]^+$, 215

Elemental Analysis for $C_{15}H_{16}N_2O_2$

Calcd.: C,70.29; H,6.29; N,10.93

Found : C,69.17; H,6.32; N,10.74

Preparation 5

To a solution of 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone (610 mg) in acetic acid (5 ml) was added 30% hydrogen bromide solution in acetic acid (0.5 ml). Under ice-cooling, pyridinium tribromide (915 mg) was added. The mixture was stirred for 30 minutes at the same temperature and for 3 hours at ambient

temperature. The solution was poured into ice-water(50 ml) and extracted with chloroform (20 ml x 3). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 4:1, v/v) to give 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone as a solid (690 mg).
mp: 98-100°C
IR(KBr): 1707, 1660, 1587 cm^{-1}
^1H NMR($CDCl_3$,δ): 1.19(3H,d,J=6.64Hz), 1.34(3H,d,J=6.64Hz), 5.27(1H,7-plet,J=6.64Hz), 6.25(1H,s), 6.95(1H,d,J=9.70Hz), 7.26-7.69(4H,m), 8.05-8.10(2H,m)
APCI/MS: 336 and 334$[M+H]^+$, 295 and 293, 257, 215
Elemental Analysis for $C_{15}H_{15}BrN_2O_2$
Calcd.: C,53.75; H,4.51; N,8.36
Found : C,53.65; H,4.53; N,8.31

Preparation 6

To a mixture of maleic hydrazide (200 g) and HMDS (1,1,1,3,3,3-hexamethyldisilazane, 576 g) in toluene (800 ml) as solvent was added dropwise sulfuric acid (17.5 g). The mixture was heated to reflux over 1.5 hours. After cooling to 20°C, the mixture was evaporated under reduced pressure. To the residue were added propylene carbonate (400 ml) and 2-propyl iodide (607 g), and then the mixture was heated to 95°C. The reaction continued for 3 hours maintaining the temperature of 95-110°C for 3 hours. Ethyl acetate (200 ml) was added to the mixture after the mixture was cooled to 30°C, and then the mixture was quenched by water (2000 ml) in one portion. The resulting mixture was stirred for 15 minutes at the ambient temperature then below 10°C. After stirring for 1 hour at 3-10°C, the precipitate was collected, washed with ethyl acetate (cooled, 300 ml) and dried under reduced pressure to give 6-hydroxy-2-isopropyl-3(2H)-pyridazinone as a yellowish solid (225.6 g).
^1H NMR(200 MHz, DMSO-d_6, δ): 1.24(6H,d,J=6.6 Hz), 4.98-5.12(1H,m), 6.87(1H,d,J=9.7 Hz), 7.03(1H,d,J=9.7 Hz)

Preparation 7

To a mixture of maleic hydrazide (10 g) and HMDS (21.6 g) in toluene (30 ml) as solvent was added dropwise sulfuric acid (0.88 g). The mixture was heated for one and a half hours at 100 ℃. After cooling, the mixture was evaporated under reduced pressure. To the residue were added propylene carbonate (20 ml) and methyl iodide (25.32 g), and then the mixture was refluxed for 2 hours. Ethyl acetate (40 ml) and water (100ml) were added to the mixture after the mixture was cooled to room temperature. The resulting mixture was stirred for 30 minutes at the ambient temperature. The resulting precipitate was collected, washed with ethyl acetate (20 ml) and dried under reduced pressure to give 1-methyl-1,2-dihydro-3,6-pyridazinedione as a brown crystalline (9.18 g).

^{1}H NMR(200 MHz, DMSO-d_6, δ): 3.49(1H,s), 6.91 (1H, d, J=9.6 Hz), 7.08 (1H, d, J=9.7 Hz)

API-ES/MS: 127.3 $[M+1]^+$

Preparation 8

To a mixture of maleic hydrazide (10 g) and HMDS (21.6 g) in toluene (30 ml) as solvent was added dropwise sulfuric acid (0.88 g). The mixture was heated for one and a half hours at 100 ℃. After cooling, the mixture was evaporated under reduced pressure. To the residue were added propylene carbonate (20 ml) and n-butyl iodide (32.83 g), and then the mixture was refluxed for 3 hours. Ethyl acetate (100 ml) and water (100ml) were added to the mixture after the mixture was cooled to room temperature. The resulting mixture was stirred at the ambient temperature . The separated organic layer was added with n-heptane (100ml) and the resulting mixture was stirred under cooling to 5 ℃. The resulting precipitate was collected and washed with a mixture of ethyl acetate (10 ml) and n-heptane (10ml), then dried under reduced pressure to give 2-n-butyl-6-hydroxy-3(2H)-pyridazinone as a yellowish white crystalline (11.86 g).

^{1}H NMR(200 MHz, DMSO-d_6, δ): 0.89(3H,t, J=7.2Hz), 1.19-1.37 (2H, m),

1.56-1.71 (2H, m), 3.86 (2H, t, J=7.3Hz), 6.87 (1H, d, J=9.8 Hz), 7.03 (1H, d, J=13.9Hz), 11.07 (1H, s)
API/MS: 169.3 $[M+1]^+$

Preparation 9

To a mixture of maleic hydrazide (10 g) and HMDS (21.6 g) in toluene (30 ml) as solvent was added dropwise sulfuric acid (0.88 g). The mixture was heated for one and a half hours at 100 ℃. After cooling, the mixture was evaporated under reduced pressure. To the residue were added propylene carbonate (20 ml) and benzyl bromide (30.5 g), and then the mixture was refluxed for 2 hours. Water (100 ml) was added to the mixture after the mixture was cooled to room temperature, and then the mixture was cooled to 5 ℃. The resulting precipitate was collected, washed with a mixture of water (30ml) and acetone (20ml), then dried under reduced pressure to give 2-benzyl-6-hydroxy-3(2H)-pyridazinone as a yellowish white crystalline (17.64 g).
^{1}H NMR(200 MHz, DMSO-d_6, δ): 5.08 (2H, s), 6.96 (1H, d, J=9.8Hz), 7.09 (1H, d, J=9.8Hz), 11.18 (1H, s)
API-ES/MS: 203.2 $[M+1]^+$

Preparation 10

To a mixture of maleic hydrazide (10 g) and HMDS (21.6 g) in toluene (30 ml) as solvent was added dropwise sulfuric acid (0.88 g). The mixture was heated for one and a half hours at 100 ℃. After cooling, the mixture was evaporated under reduced pressure. To the residue were added propylene carbonate (20 ml) and ethyl bromoacetate (29.80 g), and then the mixture was refluxed for 2 hours. Water (100 ml) was added to the mixture after the mixture was cooled to room temperature, and then the mixture was cooled to 5 ℃. The resulting precipitate was collected, washed with a mixture of water (30ml) and acetone (20ml), then dried under reduced pressure to give ethyl 3-hydroxy-6-oxo-1(6H)- pyridazinylacetate as a white crystalline (14.48 g).

^{1}H NMR(200 MHz, DMSO-d_6, δ): 1.20 (3H, t, J=7.2Hz), 4.14 (2H, q, J=7.1Hz), 4.64 (2H, s), 6.95 (1H, d, J=9.7Hz), 7.13 (1H, d, J=9.9Hz), 11.23 (1H, s)

API-ES/MS: 199.1 $[M+1]^+$

Preparation 11

To a solution of 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone (15.12 g) in acetic acid (90 mL) was added 30% hydrogen bromide solution in acetic acid (9 mL). Under ice-cooling, pyridinium tribromide (22.64 g) was added to the mixture. The mixture was stirred for 30 minutes at the same temperature and for 3 hours at ambient temperature. The mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with water, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 80 : 20 v/v) to give 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone as a solid (16.27 g).

m.p.: 98-100℃ (diisopropyl ether - n-hexane)

IR (KBr) : 1707, 1660, 1587 cm^{-1}

APCI/MS : 336 and 334$(M+Na)^+$

^{1}H NMR ($CDCl_3$, δ) : 1.19(3H, d, J=6.64 Hz), 1.34(3H, d, J=6.64 Hz), 5.27(1H, 7-plet, J=6.64 Hz), 6.25(1H, s), 6.95(1H, d, J=9.70 Hz), 7.26-7.69(4H, m), 8.05-8.10(2H, m)

Elemental Analysis for $C_{15}H_{15}BrN_2O_2$

Calcd. C: 53.73; H: 4.51; N: 8.36

Found C: 53.65; H: 4.53; N: 8.31

Preparation 12

A mixture of 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone (11.93 g) and ethyl amino(thioxo)acetate (7.11 g) in ethanol (150 mL) was refluxed for 80 hours. After evaporation of ethanol, the mitxure was dissolved in chloroform and washed with

water, an aqueous sodium hydrogen carbonate solution and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 60 : 40, v/v) to give ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate as a solid (5.52 g).

m.p.: 153-154℃ (acetone - n-hexane)

IR (KBr) : 1711, 1668, 1589 cm^{-1}

ESI/MS : 392$(M+Na)^+$, 370$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.64 Hz), 1.46(3H, t, J=7.12 Hz), 4.52(2H, q, J=6.64 Hz), 5.32(1H, 7-plet, J=6.64 Hz), 6.71(1H, d, J=9.70 Hz), 6.95(1H, d, J=9.70 Hz), 7.40-7.62(3H, m), 7.51-7.58(2H, m)

Elemental Analysis for $C_{19}H_{19}N_3O_3S$

Calcd. C: 61.77; H: 5.18; N: 11.37

Found C: 61.61; H: 5.16; N: 11.35

Preparation 13

Ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate was prepared as a solid (69.28 g), from 6-(1-chloro-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone (90.0 g) and ethyl amino(thioxo)acetate (53.5 g) in a manner similar to Preparation 12

m.p.: 153-154℃ (acetone - n-hexane)

IR (KBr) : 1711, 1668, 1589 cm^{-1}

ESI/MS : 392$(M+Na)^+$, 370$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.64 Hz), 1.46(3H, t, J=7.12 Hz), 4.52(2H, q, J=6.64 Hz), 5.32(1H, 7-plet, J=6.64 Hz), 6.71(1H, d, J=9.70 Hz), 6.95(1H, d, J=9.70 Hz), 7.40-4762(3H, m), 7.51-7.58(2H, m)

Elemental Analysis for $C_{19}H_{19}N_3O_3S$

Calcd. C: 61.77; H: 5.18; N: 11.37

Found C: 61.61; H: 5.16; N: 11.35

Preparation 14

Ethyl 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-

pyridazinyl)-1,3-thiazole-2-carboxylate wase obtained in a manner similar to Preparation 12.

m.p.: 193-194℃ (acetone - diisopropyl ether)

IR (KBr) : 1689, 1649, 1585, 1535 cm^{-1}

APCI/MS : 797$(2M+Na)^+$, 410$(M+Na)^+$, 388$(M+H)^+$,

^1H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.66 Hz), 1.46(3H, t, J=7.14 Hz), 4.52(2H, q, J=7.14 Hz), 5.33(1H, 7-plet, J=6.66 Hz), 6.75(1H, d, J=9.60 Hz), 6.96(1H, d, J=9.60 Hz), 7.08-7.19(2H, m), 7.51-7.59(2H, m)

Elemental Analysis for $C_{19}H_{18}FN_3O_3S$

Calcd. C: 58.90; H: 4.68; N: 10.85

Found C: 59.04; H: 4.68; N: 10.90

Preparation 15

Ethyl 4-(2-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate wase obtained in a manner similar to Preparation 12.

m.p.: 139.5-141℃ (acetone - n-hexane)

IR (KBr) : 1712, 1668, 1589 cm^{-1}

ESI/MS : 797$(2M+Na)^+$, 410$(M+Na)^+$, 388$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.33(6H, d, J=6.66 Hz), 1.46(3H, t, J=7.12 Hz), 4.52(2H, q, J=7.12 Hz), 5.29(1H, 7-plet, J=6.66 Hz), 6.76(1H, d, J=9.58 Hz), 7.00(1H, d, J=9.58 Hz), 7.07-7.17(1H, m), 7.24-7.32(1H, m), 7.39-7.50(1H, m), 7.57-7.67(1H, m)

Elemental Analysis for $C_{19}H_{18}FN_3O_3S$

Calcd. C: 58.90; H: 4.68; N: 10.85

Found C: 59.15; H: 4.72; N: 10.78

Preparation 16

Ethyl 4-(3-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate wase obtained in a manner similar to Preparation 12.

m.p.: 154-155℃ (acetone - n-hexane)

IR (KBr) : 1712, 1668, 1587 cm^{-1}

ESI/MS : 797$(2M+Na)^+$, 410$(M+Na)^+$, 388$(M+H)^+$

^{1}H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.62 Hz), 1.47(3H, t, J=7.90 Hz), 4.52(2H, q, J=7.90 Hz), 5.33(1H, 7-plet, J=6.62 Hz), 6.76(1H, d, J=9.70 Hz), 6.99(1H, d, J=9.70 Hz), 7.09-7.19(1H, m), 7.26-7.42(3H, m)

Elemental Analysis for $C_{19}H_{18}FN_3O_3S$

Calcd. C: 58.90; H: 4.68; N: 10.85

Found C: 59.13; H: 4.72; N: 10.88

Preparation 17

Ethyl 4-(3-chlorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate wase obtained in a manner similar to Preparation 12.

m.p.: 134-136℃ (acetone - n-hexane)

IR (KBr) : 1728, 1668, 1591 cm^{-1}

ESI/MS : 831 and 829$(2M+Na)^+$, 428 and 426$(M+Na)^+$

^{1}H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.61 Hz), 1.47(3H, t, J=7.08 Hz), 4.53(2H, q, J=7.08 Hz), 5.33(1H, 7-plet, J=6.61 Hz), 6.77(1H, d, J=9.62 Hz), 7.00(1H, d, J=9.62 Hz), 7.30-7.46(3H, m), 7.61-7.63(1H, m)

Elemental Analysis for $C_{19}H_{18}ClN_3O_3S$

Calcd. C: 56.50; H: 4.49; N: 10.40

Found C: 56.59; H: 4.50; N: 10.48

Preparation 18

Ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate wase obtained in a manner similar to Preparation 12.

m.p.: >250℃ (ethanol)

IR (KBr) : 1711, 1678, 1657, 1583 cm^{-1}

ESI/MS : 350$(M+Na)^+$, 328$(M+H)^+$

^{1}H NMR (DMSO-d_6, δ) : 1.35(3H, t, J=7.08 Hz), 4.42(2H, q, J=7.08 Hz), 6.84(1H, d, J=9.90 Hz), 7.06(1H, d, J=9.90 Hz), 7.46-7.59(5H, m), 13.44(1H, br.s)

Elemental Analysis for $C_{16}H_{13}N_3O_3S \cdot 0.4H_2O$

Calcd. C: 57.44; H: 4.16; N: 12.56

Found C: 57.25; H: 3.87; N: 12.52

Preparation 19

To a solution of 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone (20.01 g) in dichloromethane (4.8 mL) was dropwise added sulfuryl chloride (6.59 mL) under reflux, and the mixture was refluxed for 30 minutes. The solution was poured into dichloromethane (40 mL). The resulting mixture was washed with water, an aqueous sodium hydrgencarbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 75 : 25, v/v) to give 6-(1-chloro-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone as a solid (21.38 g).

m.p.: 86.5-87.5℃ (n-hexane)

IR (KBr) : 1711, 1660, 1589 cm^{-1}

ESI/MS : 603 and 605$(2M+Na)^+$, 313 and 315$(M+Na)^+$, 291 and 293$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.28(3H, d, J=6.63 Hz), 1.32(3H, d, J=6.63 Hz), 5.26(1H, 7-plet, J=6.63 Hz), 6.24(1H, s), 6.94(1H, d, J=9.66 Hz), 7.26-7.68(4H, m), 8.03-8.09(2H, m)

Elemental Analysis for $C_{15}H_{15}ClN_2O_2$

Calcd. C: 61.97; H: 5.20; N: 9.63

Found C: 62.15; H: 5.17; N: 9.70

Preparation 20

In the presence of dichlorobis(triphenylphosphine)palladium(II) (1.47 g) and copper(I) iodide (1.47 g), triethylamine (14.67 mL) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (20.10 g) and ethynyl(trimethyl)silane (24.81 mL) in tetrahydrofuran (300 mL) under ice-cooling for 2 hour. The mixture was stirred for 3 hours at ambient temperature. The reaction mixture was poured into a mixture of water and ethyl acetate. An organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 90 : 10, v/v) to give

2-isopropyl-6-[(trimethylsilyl)ethynyl]-3(2H)-pyridazinone as a solid (16.10 g).

mp : 61-62.5℃ (n-hexane)

IR (KBr) : 2160, 1664, 1587 cm^{-1}

ESI/MS : 491($2M+Na)^+$, 257$(M+Na)^+$, 235$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.27(9H, s), 1.37(6H, d, J=6.64 Hz), 5.29(1H, 7-plet, J=6.64 Hz), 6.81(1H, d, J=9.54 Hz), 7.21(1H, d, J=9.54 Hz), 7.51-7.61(2H, m)

Elemental Analysis for $C_{12}H_{18}N_2OSi$

Calcd. C: 61.50; H: 7.74; N: 11.95

Found C: 61.25; H: 7.82; N: 12.00

Preparation 21

To a solution of 2-isopropyl-6-[(trimethylsilyl)ethynyl]-3(2H)-pyridazinone and benzyltriethyl-ammonium chloride (0.52 g) in a mixture of tetrahydrofuran (45 mL) and acetonitrile (45 mL) was added dropwise 12N aqueous sodium hydroxide solution (60 mL) under ice-cooling. After stirring for 30 minutes, the mixture was acidified with concentrated hydrochloric acid under ice-cooling. The mixture was extracted with chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 80 : 20, v/v) to give 6-ethynyl-2-isopropyl-3(2H)-pyridazinone as a solid (10.42 g).

mp : 103-104℃ (acetone - n-hexane)

IR (KBr) : 3194, 2108, 1655, 1587 cm^{-1}

ESI/MS : 185$(M+Na)^+$, 163$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.64 Hz), 3.19(1H, s), 5.31(1H, 7-plet, J=6.64 Hz), 6.85(1H, d, J=9.52Hz), 7.22(1H, d, J=9.52 Hz)

Elemental Analysis for $C_9H_{10}N_2O$

Calcd. C: 66.65; H: 6.21; N: 17.27

Found C: 66.92; H: 6.28; N: 17.36

Preparation 22

In the presence of dichlorobis(triphenylphosphine)palladium(II) (0.42 g) and copper(I) iodide (0.42 g), triethylamine (3.9 mL) was added dropwise to a mixture of 6-ethynyl-2-isopropyl-3(2H)-pyridazinone (3.25 g) and 1-fluoro-4-iodobenzene (6.67 g) in dioxane (60 mL) for 0.5 hour at 75-80 ℃. The mixture was stirred for 1.5 hours at 75-80℃. After cooling, a mixture of water and ethyl acetate was added to the reaction mixture. An organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 70 : 30, v/v) to give 6-[(4-fluorophenyl)-ethynyl]-2-isopropyl-3(2H)-pyridazinone as a solid (3.81 g).

mp : 105.5-106.5℃ (n-hexane)

IR (KBr) : 2208, 1664, 1587 cm^{-1}

ESI/MS : 535$(2M+Na)^+$, 279$(M+Na)^+$, 257$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.64 Hz), 5.33(1H, 7-plet, J=6.64 Hz), 6.87(1H, d, J=9.57 Hz), 7.01-7.14(2H, m), 7.28(1H, d, J=9.57 Hz), 7.51-7.61(2H, m)

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd. C: 70.30; H: 5.11; N: 10.93

Found C: 70.33; H: 5.34; N: 11.05

Preparation 23

6-[(2-Fluorophenyl)-ethynyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 22.

m.p.: 84.5-86℃ (diisopropyl ether - n-hexane)

IR (KBr) : 2224, 1660, 1644, 1583 cm^{-1}

ESI/MS : 535$(2M+Na)^+$, 279$(M+Na)^+$, 257$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.41(6H, d, J=6.62 Hz), 5.34(1H, 7-plet, J=6.62 Hz), 6.88(1H, d, J=9.52 Hz), 7.12-7.20(2H, m), 7.32(1H, d, J=9.52 Hz), 7.33-7.41(1H, m), 7.52-7.60(1H, m)

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd. C: 70.30; H: 5.11; N: 10.93

Found C: 70.38; H: 5.14; N: 10.95

Preparation 24

6-[(3-Fluorophenyl)-ethynyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 22.

m.p.: 95.5-96.5℃ (acetone - n-hexane)

IR (KBr) : 2220, 1660, 1606, 1585 cm^{-1}

ESI/MS : 535$(2M+Na)^+$, 279$(M+Na)^+$, 257$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.41(6H, d, J=6.62 Hz), 5.34(1H, 7-plet, J=6.62 Hz), 6.88(1H, d, J=9.52 Hz), 7.12-7.20(2H, m), 7.32(1H, d, J=9.52 Hz), 7.33-7.41(1H, m), 7.52-7.60(1H, m)

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd. C: 70.30; H: 5.11; N: 10.93

Found C: 70.22; H: 5.16; N: 10.94

Preparation 25

In the presence of dichlorobis(triphenylphosphine)palladium(II) (0.42 g) and copper(I) iodide (0.42 g), triethylamine (3.9 mL) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (5.73 g) and 1-ethynyl-4-fluorobenzene (3.65 g) in dioxane (60 mL) for 0.5 hour at 75-80℃. The mixture was stirred for 1.5 hours at 75-80℃. After cooling, water and chloroform were added to the reaction mixture. An organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 70 : 30, v/v) to give 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone as a solid (4.22 g).

mp : 105.5-106.5℃ (n-hexane)

IR (KBr) : 2208, 1664, 1587 cm^{-1}

ESI/MS : 535$(2M+Na)^+$, 279$(M+Na)^+$, 257$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.64 Hz), 5.33(1H, 7-plet, J=6.64 Hz), 6.87(1H, d, J=9.57 Hz), 7.01-7.14(2H, m), 7.28(1H, d, J=9.57 Hz), 7.51-7.61(2H, m)

Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd. C: 70.30; H: 5.11; N: 10.93

Found C: 70.33; H: 5.34; N: 11.05

Preparation 26

6-[(3-Chlorophenyl)-ethynyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to preparation 25.

m.p.: 94-95℃ (heptane)

IR (KBr) : 1664, 1589 cm^{-1}

ESI/MS : 569 and 567$(2M+Na)^+$, 297 and 295$(M+Na)^+$, 275 and 273$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.65 Hz), 5.33(1H, 7-plet, J=6.65 Hz), 6.88(1H, d, J=9.54 Hz), 7.25-7.48(4H, m), 7.55-7.58(1H, m)

Elemental Analysis for $C_{15}H_{13}ClN_2O$

Calcd. C: 66.06; H: 4.80; N: 10.27

Found C: 66.10; H: 4.83; N: 10.27

Preparation 27

To a mixture of sulfuric acid (6 mL) and acetic acid (15 mL) was added 6-[(4-fluorophenyl)-ethynyl]-2-isopropyl-3(2H)-pyridazinone (3.00 g), and the mixture was heated for 40 minutes at 100-105℃. The solution was poured into a mixuture of ice (90 g) and sodium carbonate (25.4 g). The resulting mixture was extracted with ethyl acetate (24 mL x 2), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 30 : 70, v/v) to give 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone as a solid (451 mg).

mp : 67-68℃ (n-hexane)

IR (KBr) : 1689, 1660, 1596 cm^{-1}

APCI/MS : 275$(M+H)^+$, 233

^1H NMR ($CDCl_3$, δ) : 1.32(6H, d, J=6.62 Hz), 4.28(2H, s), 5.29(1H, 7-plet, J=6.62 Hz), 6.89(1H, d, J=9.50 Hz), 7.11-7.23(3H, m), 8.04-8.13(2H, m)

Elemental Analysis for $C_{15}H_{15}FN_2O_2$

Calcd. C: 65.68; H: 5.51; N: 10.21
Found C: 65.72; H: 5.65; N: 10.21

Preparation 28

6-[2-(2-Fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 27.
IR (Neat) : 1685, 1664, 1593 cm^{-1}
ESI/MS : 571$(2M+Na)^+$, 297$(M+Na)^+$, 275$(M+H)^+$
^1H NMR ($CDCl_3$, δ) : 1.32(6H, d, J=6.65 Hz), 4.28(2H, s), 5.29(1H, 7-plet, J=6.65 Hz), 6.89(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.40-7.49(1H, m), 7.55-7.62(1H, m), 7.89-7.95(1H, m), 8.02-8.04(1H, m)

Preparation 29

6-[2-(3-Fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 27.
m.p.: 80-81℃ (diisopropyl ether - n-hexane)
IR (KBr) : 1680, 1658, 1591 cm^{-1}
ESI/MS : 274$(2M+Na)^+$, 297$(M+Na)^+$, 275$(M+H)^+$
^1H NMR ($CDCl_3$, δ) : 1.32(6H, d, J=6.60 Hz), 4.29(2H, s), 5.29(1H, 7-plet, J=6.60 Hz), 6.89(1H, d, J=9.48 Hz), 7.18(1H, d, J=9.48 Hz), 7.26-7.33(1H, m), 7.43-7.53(1H, m), 7.70-7.77(1H, m), 7.80-7.86(1H, m)
Elemental Analysis for $C_{15}H_{15}FN_2O_2$
Calcd. C: 65.68; H: 5.51; N: 10.21
Found C: 65.73; H: 5.61; N: 10.24

Preparation 30

6-[2-(3-Chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 27.
m.p.: 85-86℃ (diisopropyl ether - n-hexane)
IR (KBr) : 1676, 1658, 1591 cm^{-1}
ESI/MS : 605 and 603$(2M+Na)^+$, 315 and 313$(M+Na)^+$, 293 and 291$(M+H)^+$

^{1}H NMR ($CDCl_3$, δ) : 1.32(6H, d, J=6.65 Hz), 4.28(2H, s), 5.29(1H, 7-plet, J=6.65 Hz), 6.89(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.40-7.49(1H, m), 7.55-7.62(1H, m), 7.89-7.95(1H, m), 8.02-8.04(1H, m)

Elemental Analysis for $C_{15}H_{15}ClN_2O_2$

Calcd. C: 61.97; H: 5.20; N: 9.63

Found C: 62.10; H: 5.25; N: 9.68

Preparation 31

To a solution of 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone (2.40 g) in dichloromethane (4.8 mL) was dropwise added a solution of sulfuryl chloride (1.24 g) in dichloromethane (0.8 mL) under reflux, and the mixture was refluxed for 30 minutes. The solution was poured into dichloromethane (40 mL). The mixture was washed with water, an aqueous sodium hydrgencarbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 80 : 20, v/v) to give 6-[1-chloro-2-(4- fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone as a solid (2.17 g).

mp : 86.5-88℃ (n-hexane)

IR (KBr) : 1709, 1658, 1592 cm^{-1}

ESI/MS : 641 and 639$(2M+Na)^+$, 333 and 331$(M+Na)^+$

^{1}H NMR ($CDCl_3$, δ) : 1.28(3H, d, J=6.60 Hz), 1.37(3H, d, J=6.60 Hz), 5.26(1H, 7-plet, J=6.60 Hz), 6.17(1H, s), 6.94(1H, d, J=9.70 Hz), 6.96-7.27(2H, m), 7.48(1H, d, J=9.70 Hz), 8.05-8.15(2H, m)

Elemental Analysis for $C_{15}H_{14}ClFN_2O_2$

Calcd. C: 58.36; H: 4.57; N: 9.07

Found C: 58.54; H: 4.59; N: 9.07

Preparation 32

6-[1-Chloro-2-(2-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 31.

IR (Neat) : 1666, 1595 cm^{-1}

ESI/MS : 641 and 639($2M+Na)^+$, 333 and 331($M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.14(3H, d, J=6.62 Hz), 1.23(3H, d, J=6.62 Hz), 5.19(1H, 7-plet, J=6.62 Hz), 6.19(1H, s), 6.94(1H, d, J=9.60 Hz), 7.09-7.20(1H, m), 7.25-7.34(1H, m), 7.43(1H, d, J=9.60 Hz), 7.52-7.75(1H, m), 7.92-7.82(1H, m)

Elemental Analysis for $C_{15}H_{14}ClFN_2O_2$

Calcd. C: 58.36; H: 4.57; N: 9.07

Found C: 58.09; H: 4.68; N: 9.01

Preparation 33

6-[1-Chloro-2-(3-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 31.

m.p.: 65.5-66.5℃ (n-hexane)

IR (KBr) : 1714, 1664, 1589 cm^{-1}

ESI/MS : 641 and 639($2M+Na)^+$, 333 and 331($M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.27(3H, d, J=6.68 Hz), 1.32(3H, d, J=6.68 Hz), 5.26(1H, 7-plet, J=6.68 Hz), 6.18(1H, s), 6.95(1H, d, J=9.68 Hz), 7.27-7.52(3H, m), 7.72-7.88(2H, m)

Elemental Analysis for $C_{15}H_{14}ClFN_2O_2$

Calcd. C: 58.36; H: 4.57; N: 9.07

Found C: 58.44; H: 4.42; N: 9.09

Preparation 34

6-[1-Chloro-2-(3-chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Preparation 31.

IR (Neat) : 1697, 1670, 1593 cm^{-1}

ESI/MS : 673 and 671($2M+Na)^+$, 349 and 347($M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(3H, d, J=6.64 Hz), 1.33(3H, d, J=6.64 Hz), 5.26(1H, 7-plet, J=6.64 Hz), 6.19(1H, s), 6.95(1H, d, J=9.70 Hz), 7.41-7.50(2H, m), 7.57-7.63(1H, m), 7.91-7.97(1H, m), 8.03-8.06(1H, m)

Elemental Analysis for $C_{15}H_{14}Cl_2N_2O_2$

Calcd. C: 55.40; H: 4.34; N: 8.61

Found C: 55.47; H: 4.53; N: 8.48

Preparation 35

Trifluoromethanesulfonic anhydride (3.55 mL) was added dropwise to a solution of 3,6-dihydroxypyridazine (2.25 g) in pyridine (50 mL) under ice-cooling. The mixture was stirred for one hour under ice-cooling and for 2 hours at ambient temperature. After addition of methanol (1 mL) under ice-cooling, pyridine was evaporated under reduced pressure to give a syrup. The syrup was dissolved in ethyl acetate. The mixture was washed with water, 1N-hydrochloric acid, an aqueous sodium hydrogencarbonate solution and brine. The mixture was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 60 : 40 and 40 : 60, v/v) to give 6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate as a solid (4.10 g).

m.p.: 130-131.5℃ (acetone - n-hexane)

IR (KBr) : 3080, 2985, 2881, 1703, 1641, 1597 cm^{-1}

ESI/MS : 243$(M-H)^-$

^1H NMR (DMSO-d_6, δ) : 7.18(1H, d, J=10.05Hz), 7.76(1H, d, 10.05Hz), 13.27(1H, s)

Elemental Analysis for $C_5H_3F_3N_2O_4S$

Calcd. C: 24.60; H: 1.24; N: 11.47

Found C: 24.63; H: 1.16; N: 11.43

Preparation 36

Under nitrogen atmosphere, bis(trimethylsilyl)acetamide (5.0 mL) was added to a suspension of 6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (5.00 g) in tetrahydrofuran (10 mL), and the mixture was stirred at ambient temperature for 15 minutes. To the mixture were added ethynylbenzene (2.30 g), dichlorobis(triphenylphosphine)palladium(II) (72 mg) and copper(I) iodide (20 mg). A solution of triethylamine (3.14 mL) in tetrahydrofuran (2.5 mL) was added dropwise to the mixture under reflux. The reaction mixture was refluxed for one hour. After cooling,

the mixture was poured into water (100 mL) to afford a solid. The solid was collected by filtration, dried over phosphorous petoxide under reduced pressure and recrystallized from a mixture of methanol and diisopropyl ether to give 6-(phenylethynyl)-3(2H)-pyridazinone as a solid (2.48 g).

m.p.: 190-192℃ (methanol - diisopropyl ether)

IR (KBr) : 2222, 1664, 1647 cm^{-1}

ESI/MS : 415$(2M+Na)^+$, 219$(M+Na)^+$, 197$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 6.94(1H, d, J=8.64 Hz), 7.42-7.50(3H, m), 7.55-7.63(3H, m), 13.36(1H, br.s)

Elemental Analysis for $C_{12}H_8N_2O$

Calcd. C: 73.46; H: 4.11; N: 14.28

Found C: 73.33; H: 4.10; N: 14.13

Preparation 37

To a mixture of sulfuric acid (11.0 mL) and acetic acid (27.5 mL) was added 6-(phenylethynyl)-3(2H)-pyridazinone (5.50 g), and the mixture was heated for 30 minutes at 100-105℃. The solution was poured into a mixuture of ice (37.3 g) and sodium carbonate (165 g) and warmed at 30℃ to obtain a solid. The solid was collected by filtration, dried over phosphorous pentoxide and purified by a column chromatography on silica gel (methanol : chloroform = =2 : 98, v/v) to give 6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone as a solid (3.86 g).

m.p.: 178-179℃ (chloroform - n-hexane)

IR (KBr) : 1678, 1660, 1603 cm^{-1}

ESI/MS : 451$(2M+Na)^+$, 237$(M+Na)^+$, 215$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 4.30(2H, s), 6.95(1H, d, J=9.76 Hz), 7.29(1H, d, J=9.76 Hz), 7.49-7.54(2H, m), 7.60-7.65(1H, m), 7.97-8.06(2H, m), 10.52(1H, br.s)

^1H NMR (DMSO-d_6, δ) : 4.43(2H, s), 6.86(1H, d, J=9.75 Hz), 7.38(1H, d, J=9.75 Hz), 7.51-7.60(2H, m), 7.64-7.73(1H, m), 8.00-8.05(2H, m)

Elemental Analysis for $C_{12}H_{10}N_2O_2$

Calcd. C: 67.28; H: 4.70; N: 13.08

Found C: 67.36; H: 4.69; N: 13.23

Preparation 38

To a solution of 6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone (1.00 g) in acetic acid (9 mL) was added 30% hydrogen bromide solution in acetic acid (1 mL). Under ice-cooling, pyridinium tribromide (1.79 g) was added to the mixture. The mixture was stirred for 30 minutes at the same temperature and for 20 hours at ambient temperature to obtain a solid. The solid was collected by filtration and dissolved in chloroform (30 mL). The mixture was washed with an aqueous sodium hydrogencarbonate solution, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was recrystallized from a mixture of acetone and diisopropyl ether to give 6-(1-bromo-2-oxo-2-phenylethyl)-3(2H)-pyridazinone as a solid (1.01 g).

m.p.: 140-141.5℃ (acetone - diisopropyl ether)

IR (KBr) : 1682, 1666, 1595 cm^{-1}

ESI/MS : 315 and 317$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 6.21(1H, s), 7.03(1H, d, J=9.94 Hz), 7.48-7.66(3H, m), 7.78(1H, d, J=9.94 Hz), 8.02-8.08(2H, m), 11.81(1H, br.s)

^1H NMR (DMSO-d_6, δ) : 6.98(1H, d, J=10.08 Hz), 7.03(1H, s), 7.51-7.77(4H, m), 8.02-8.07(2H, m), 13.14(1H, br.s)

Elemental Analysis for $C_{12}H_9BrN_2O_2$

Calcd. C: 49.17; H: 3.09; N: 9.56

Found C: 49.53; H: 3.08; N: 9.64

Preparation 39

To a solution of 6-(phenylethynyl)-3(2H)-pyridazinone (100 mg) in dimethylformamide (0.5 mL) was added sodium hydride (60 % in oil) (21 mg), and the mixture was stirred for 30 minutes at 50-55℃. 2-Iodopropane (0.056 mL) was added to the mixture, and the mixture was stirred for 3 hours at 50-55℃. The reaction mixture was diluted with ethyl acetate. The mixture was washed with water and brine, dried over magnesium sulfate and concetrated under reduced pressure to obtain a residue. The residue was purified by a preparative TLC on

silica gel (n-hexane : ethyl acetate = 60 : 40 v/v) to give 2-isopropyl-6-(phenylethynyl)-3(2H)-pyridazinone as a solid (93 mg).

mp : 75.5-77℃ (heptane)

IR (KBr) : 2218, 1669, 1583 cm^{-1}

APCI/MS : 239$(M+H)^+$, 197

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.65 Hz), 5.33(1H, 7-plet, J=6.65 Hz), 6.87(1H, d, J=9.57 Hz), 7.26-7.42(4H, m), 7.52-7.60(2H, m)

Elemental Analysis for $C_{15}H_{14}N_2O$

Calcd. C: 75.61; H: 5.92; N: 11.76

Found C: 75.79; H: 5.88; N: 11.74

Preparation 40

To a solution of ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (1.64 g) in dimethylformamide (5 mL) was added sodium hydride (60 % in oil) (210 mg), and the mixture was stirred at 50-55℃ for 30 minutes. Iodomethane (0.374 mL) was added to the mixture, and the mixture was stirred for 20 hours at ambient temperature. The mixture was poured into water (20 mL) to give a solid. The solid was collected by filtration, dried over phosphorous pentoxide and purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give ethyl 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate as a solid (1.56 g).

m.p.: 157.5-159℃ (chloroform - diisopropyl ether)

IR (KBr) : 1707, 1668 cm^{-1}

ESI/MS : 705$(2M+Na)^+$, 364$(M+Na)^+$, 342$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.46(3H, t, J=7.12 Hz), 3.85(3H, s), 4.52(2H, q, J=7.12 Hz), 6.73(1H, d, J=9.72 Hz), 6.96(1H, d, J=9.72 Hz), 7.41-7.45(3H, m), 7.53-7.57(2H, m)

Elemental Analysis for $C_{17}H_{15}N_3O_3S$

Calcd. C: 59.81; H: 4.43; N: 12.31

Found C: 59.72; H: 4.35; N: 12.28

Preparation 41

To a solution of ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (1.64 g) in dimethylformamide (5 mL) was added sodium hydride (60 % in oil) (210 mg), and the mixture was stirred for 30 minutes at 50-55℃. Iodoethane (0.481 mL) was added to the mixture, and the mixture was stirred for 3 hours at 50-55℃. The mixture was poured into water (20 mL) to obtain a solid. The solid was collected by filtration, dried over phosphorous pentoxide and purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 70 : 30, v/v) to give ethyl 5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate as a solid (1.62 g).

m.p.: 144-146℃ (chloroform - diisopropyl ether)

IR (KBr) : 1707, 1666 cm^{-1}

ESI/MS : 733$(2M+Na)^+$, 378$(M+Na)^+$, 356$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.44(3H, t, J=7.20 Hz), 1.46(3H, t, J=7.12 Hz), 4.26(2H, q, J=7.20 Hz), 4.52(2H, q, J=7.12 Hz), 6.73(1H, d, J=9.72 Hz), 6.96(1H, d, J=9.72 Hz), 7.41-7.45(3H, m), 7.54-7.57(2H, m)

Elemental Analysis for $C_{18}H_{17}N_3O_3S$

Calcd. C: 60.83; H: 4.82; N: 11.82

Found C: 60.91; H: 4.73; N: 11.89

Preparation 42

Ethyl 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate was obtained in a manner similar to Preparation 41.

m.p.: 124.5-126℃ (chloroform - diisopropyl ether)

IR (KBr) : 1709, 1664 cm^{-1}

ESI/MS : 761$(2M+Na)^+$, 392$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.03(3H, t, J=7.20 Hz), 1.46(3H, t, J=7.12 Hz), 1.84-1.92(2H, m), 4.17(2H, t, J=7.20 Hz), 4.51(2H, q, J=7.12 Hz), 6.73(1H, d, J=9.72 Hz), 6.95(1H, d, J=9.72 Hz), 7.41-7.45(3H, m), 7.53-7.57(2H, m)

Elemental Analysis for $C_{16}H_{13}N_3O_3S \cdot 0.5H_2O$

Calcd. C: 60.30; H: 5.33; N: 11.10

Found C: 60.29; H: 5.03; N: 11.07

Preparation 43

Ethyl 5-(1-allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate was obtained in a manner similar to Preparation 41.

m.p.: 94-95℃ (chloroform - diisopropyl ether)

IR (KBr) : 1711, 1668 cm^{-1}

ESI/MS : 757($2M+Na)^+$, 390($M+Na)^+$, 368($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.46(3H, t, J=7.12 Hz), 4.51(2H, q, J=7.12 Hz), 4.79-4.82(2H, m), 5.29-5.36(2H, m), 6.00-6.11(1H, m), 6.74(1H, d, J=9.72 Hz), 6.96(1H, d, J=9.72 Hz), 7.42-7.45(3H, m), 7.53-7.57(2H, m)

Elemental Analysis for $C_{19}H_{17}N_3O_3S \cdot 0.2H_2O$

Calcd. C: 61.51; H: 4.73; N: 11.33

Found C: 61.31; H: 4.51; N: 11.20

Preparation 44

Ethyl 5-(1-benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate was obtained in a manner similar to Preparation 41.

m.p.: 137-139℃ (chloroform - diisopropyl ether)

IR (KBr) : 1712, 1670 cm^{-1}

ESI/MS : 857($2M+Na)^+$, 440($M+Na)^+$, 418($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.46(3H, t, J=7.12 Hz), 4.52(2H, q, J=7.12 Hz), 5.35(2H, s), 6.72(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.26-7.43(3H, m), 7.48-7.55(2H, m)

Elemental Analysis for $C_{23}H_{19}N_3O_3S \cdot 0.2H_2O$

Calcd. C: 65.61; H: 4.64; N: 9.98

Found C: 65.64; H: 4.56; N: 9.80

Preparation 45

Ethyl 5-[1-(2-methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-1,3-thiazole-2-carboxylate was obtained in a manner similar to Preparation 41.

m.p.: 111-112℃ (chloroform - diisopropyl ether)

IR (KBr) : 1739, 1674 cm^{-1}

ESI/MS : 793($2M+Na)^+$, 408$(M+Na)^+$, 386$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.46(3H, t, J=7.12 Hz), 3.40(3H, s), 3.84(2H, t, J=5.58 Hz), 4.41(2H, t, J=5.58 Hz), 4.52(2H, q, J=7.12 Hz), 6.73(1H, d, J=9.76 Hz), 6.96(1H, d, J=9.76 Hz), 7.42-7.45(3H, m), 7.54-7.57(2H, m)

Elemental Analysis for $C_{19}H_{19}N_3O_4S$

Calcd. C: 59.21; H: 4.97; N: 10.90

Found C: 59.25; H: 4.93; N: 10.91

Preparation 46

Under ice-cooling, trifluoroacetic anhydride (0.163 mL) was added dropwise to a mixture of 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide (342 mg) and pyridine (0.163 mL) in dioxane (2 mL). The mixture was stirred for one hour at the same temperature and for 2 hours at ambient temperature. Water was added to the mixture to give a solid. The solid collected by filtration was dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was crysatallized from a mixture of acetone and n-hexane to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carbonitrile as a solid (271 mg).

m.p.: 135-136℃ (acetone - n-hexane)

IR (KBr) : 2229, 1670, 1589 cm^{-1}

ESI/MS : 345$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.60 Hz), 5.32(1H, 7-plet, J=6.60 Hz), 6.74(1H, d, J=9.62 Hz), 6.97(1H, d, J=9.62 Hz), 7.43-7.57(5H, m)

Elemental Analysis for $C_{17}H_{14}N_4OS$

Calcd. C: 63.34; H: 4.38; N: 17.38

Found C: 63.23; H: 4.34; N: 17.26

Example 1

A mixture of 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone (140 mg) and thiourea (48 mg) in ethanol (1.5 ml) was refluxed for 60 hours. The mixture was poured into a mixture of

chloroform (5 ml), a saturated sodium hydrogencarbonate solution (0.5 ml) and water (0.5 ml). The organic solution was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 1:4, v/v) to give 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone as a solid (97 mg).

mp: >250°C

IR(KBr): 1641, 1583, 1525 cm^{-1}

^1H NMR($CDCl_3$,δ): 1.36(6H,d,J=6.62Hz), 5.17(2H,br.s), 5.29(1H, 7-plet,J=6.62Hz), 6.61(1H,d,J=9.70Hz), 6.88(1H,d,J=9.70Hz), 7.26-7.43(3H,m), 7.45-7.53(2H,m)

APCI/MS: 345$[M+Na]^+$, 313$[M+H]^+$, 282, 257

Elemental Analysis for $C_{16}H_{16}N_4OS$

Calcd.: C,60.47; H,5.26; N,17.63

Found : C,60.45; H,5.05; N,17.58

Example 2

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (150 mg), benzoyl chloride (81 mg) and triethylamine (63.2 mg) in dimethylformamide (3 ml) was stirred overnight at ambient temperature. After 1N-hydrochloric acid was poured into the reaction mixture, the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous sodium hydrogencarbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo to give an oil, which was subjected to a column chromatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford an oil, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]- benzamide (30 mg).

mp: 126-129°C

IR(KBr): 3432, 1660, 1583 cm^{-1}

^{1}H NMR(DMSO-d_6,δ): 1.30(6H,d,J=6.6Hz), 5.15(1H,7-plet,J=6.6Hz), 6.81(1H,d,J=9.7Hz), 7.04(1H,d,J=9.7Hz), 7.35-7.7(8H,m), 8.1-8.2(2H,m), 12.96(1H,brs)

APCI/MS: 417$[M+H]^+$, 439$[M+Na]^+$

Elemental Analysis for $C_{23}H_{20}N_4O_2S \cdot 0.8H_2O$

Calcd.: C,64.11; H,5.05; N,13.00

Found : C,64.32; H,5.01; N,12.59

Example 3

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]hexanamide was obtained in a manner similar to Example 2.

mp: 129-132°C

IR(KBr): 3432, 1660, 1583 cm^{-1}

^{1}H NMR(DMSO-d_6,δ): 0.8-0.95(3H,m), 1.15-1.4(10H,m), 1.5-1.75(2H,m), 2.4-2.6(2H,m), 5.14(1H,7-plet,J=6.6Hz), 6.80(1H, d,J=9.7Hz), 7.01(1H,d,J=9.7Hz), 7.35-7.6(5H,m), 12.39(1H,brs)

APCI/MS: 411$[M+H]^+$, 433$[M+Na]^+$

Example 4

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-phenylacetamide was obtained in a manner similar to Example 2.

mp: 250-252°C

IR(KBr): 3166, 1650, 1583 cm^{-1}

^{1}H NMR(DMSO-d_6,δ): 1.25(6H,d,J=6.6Hz), 3.81(2H,s), 5.12(1H, 7-plet,J=6.6Hz), 6.80(1H,d,J=9.7Hz), 7.00(1H,d,J=9.7Hz), 7.2-7.6(10H,m), 12.68(1H,brs)

APCI/MS: 431$[M+H]^+$, 453$[M+Na]^+$

Elemental Analysis for $C_{24}H_{22}N_4O_2S \cdot 0.2H_2O$

Calcd.: C,66.40; H,5.20; N,12.91

Found : C,66.77; H,5.28; N,12.55

Example 5

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2,2-dimethylpropanamide was obtained in a manner similar to Example 2.

mp: 224-226°C

IR(KBr): 3230, 1654, 1585 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.2-1.3(15H,m), 5.13(1H,7-plet,J=6.6Hz), 6.79(1H,d,J=9.7Hz), 6.99(1H,d,J=9.7Hz), 7.35-7.6(5H,m), 12.11(1H,brs)

ESI/MS: 397$[M+H]^+$, 419$[M+Na]^+$

Elemental Analysis for $C_{21}H_{24}N_4O_2S$

Calcd.: C,63.61; H,6.10; N,14.13

Found : C,63.31; H,6.14; N,13.90

Example 6

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (200 mg), acetyl chloride (60.3 mg) and triethylamine (97.2 mg) in dimethylformamide (2 ml) was stirred overnight at ambient temperature. After 1N-hydrochloric acid was poured into the reaction mixture, the resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous sodium hydrogencarbonate solution, and dried over magnesium sulfate. The solvent was removed in vacuo to give an oil, which was subjected to a column chromatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford an oil, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-acetamide (30 mg).

mp: 202-204°C

IR(KBr): 3432, 1648, 1579 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.26(6H,d,J=6.6Hz), 2.19(3H,s), 5.13(1H, 7-plet,J=6.6Hz), 6.80(1H,d,J=9.7Hz), 7.02(1H,d,J=9.7Hz), 7.3-7.6(5H,m)

ESI/MS: 355$[M+H]^+$, 377$[M+Na]^+$

Elemental Analysis for $C_{18}H_{18}N_4O_2S$

Calcd.: C,61.00; H,5.12; N,15.81

Found : C,61.03; H,5.12; N,15.84

Example 7

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]cyclohexanecarboxamide was obtained in a manner similar to Example 2.

mp: 234-236°C

IR(KBr): 3178, 1646, 1579 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.1-1.55(11H,m), 1.55-1.9(5H,m), 5.13(1H, 7-plet,J=6.6Hz), 6.80(1H,d,J=9.7Hz), 7.00(1H,d,J=9.7Hz), 7.3-7.6(5H,m), 12.33(1H,brs)

ESI/MS: 423$[M+H]^+$, 445$[M+Na]^+$

Elemental Analysis for $C_{23}H_{26}N_4O_2S \cdot 0.1H_2O$

Calcd.: C,65.10; H,6.22; N,13.20

Found : C,65.26; H,6.42; N,12.85

Example 8

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-phenoxyacetamide was obtained in a manner similar to Example 2.

mp: 243-244°C

IR(KBr): 3399, 1697, 1666, 1589 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.26(6H,d,J=6.6Hz), 4.90(2H,s), 5.13(1H, 7-plet,J=6.6Hz), 6.80(1H,d,J=9.7Hz), 6.9-7.1(4H,m), 7.2-7.6(7H,m), 12.70(1H,brs)

ESI/MS: 447$[M+H]^+$, 469$[M+Na]^+$

Elemental Analysis for $C_{24}H_{22}N_4O_3S \cdot 0.7H_2O$

Calcd.: C,62.78; H,5.14; N,12.20

Found : C,62.89; H,4.86; N,12.03

Example 9

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(4-methoxyphenyl)acetamide was obtained in a manner similar to Example 2.

mp: 188-190°C

IR(KBr): 3191, 1648, 1581 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.26(6H,d,J=6.6Hz), 3.31(2H,s), 3.74(3H,s), 5.12(1H,7-plet,J=6.6Hz), 6.79(1H,d,J=9.7Hz), 6.85-6.95(2H,m), 6.99(1H,d,J=9.7Hz), 7.26(2H,d,J=8.7Hz), 7.35-7.55(5H,m), 12.62(1H,brs)

ESI/MS: 461$[M+H]^+$, 483$[M+Na]^+$

Elemental Analysis for $C_{25}H_{24}N_4O_3S$

Calcd.: C,65.20; H,5.25; N,12.17

Found : C,65.21; H,5.28; N,12.01

Example 10

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (200 mg) and m-tolylisocyanate (93.8 mg) in dioxane (5 ml) was stirred for 6 hours at ambient temperature. The solvent was removed in vacuo to give a pale yellow powder. The powder was recrystallized from ethanol to give N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-N'-(3-methylphenyl)urea as pale yellow crystals (100 mg).

mp: 242-243°C

IR(KBr): 3357, 1710, 1639, 1616 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.29(6H,d,J=6.6Hz), 2.31(3H,s), 5.14(1H, 7-plet,J=6.6Hz), 6.79(1H,d,J=9.8Hz), 6.8-6.95(1H,m), 6.99(1H,d,J=9.8Hz), 7.1-7.6(8H,m), 8.88(1H,s), 10.8(1H,s)

ESI/MS: 446$[M+H]^+$, 468$[M+Na]^+$

Elemental Analysis for $C_{24}H_{23}N_5O_2S$

Calcd.: C,64.44; H,5.23; N,15.66

Found : C,64.69; H,5.14; N,15.77

Example 11

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (200mg) and benzylisocyanate (93.8 mg) in dioxane (5 ml) was stirred for 6 hours at ambient temperature. The solvent was removed in vacuo to give a pale yellow powder. The powder was recrystallized from ethanol to give N-benzyl-N'-[5-(1-isopropyl-6-oxo-

1,6-dihydro-3- pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]urea as a pale yellow crystal (50 mg).

mp: 200-201°C

IR(KBr): 3307, 1698, 1639, 1575 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.27(6H,d,J=6.6Hz), 4.37(2H,d,J=5.9Hz), 5.13(1H,7-plet,J=6.6Hz), 6.77(1H,d,J=9.7Hz), 6.97(1H,d, J=9.7Hz), 7.0-7.15(1H,m), 7.2-7.55(10H,m), 10.88(1H,br)

APCI/MS: 446$[M+H]^+$

Elemental Analysis for $C_{24}H_{23}N_5O_2S$

Calcd.: C,64.44; H,5.23; N,15.66

Found : C,64.58; H,5.29; N,15.66

Example 12

N-({[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]amino}carbonyl)-4-methylbenzene- sulfonamide was obtained in a manner similar to Example 11.

mp: 172-174°C

IR(KBr): 3430, 1650, 1579 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.25(6H,d,J=6.6Hz), 2.36(3H,s), 5.10(1H, 7-plet,J=6.6Hz), 6.73(1H,d,J=9.7Hz), 6.92(1H,d,J=9.7Hz), 7.2-7.5(7H,m), 7.7-7.85(2H,m), 10.70(1H,br)

Negative ESI/MS: 508$[M-H]^-$

Example 13

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]methanesulfonamide was prepared as a brown oil in a manner similar to Example 2.

^1H NMR(DMSO-d_6,δ): 1.27(6H,d,J=6.6Hz), 3.73(3H,s), 5.14(1H, 7-plet,J=6.6Hz), 6.88(1H,d,J=9.8Hz), 7.14(1H,d,J=9.8Hz), 7.4-7.65(5H,m)

Negative ESI/MS: 389$[M-H]^-$

Example 14

A mixture of 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-

3(2H)-pyridazinone (150 mg) and 1-hexyl-2-thiourea (108 mg) in dioxane (1 ml) was stirred overnight at 80°C. Chloroform and an aqueous sodium hydrogencarbonate solution were added to the reaction mixture at ambient temperature. The separated organic layer was dried over sodium sulfate. The solvent was removed in vacuo to give a yellow powder, which was subjected to a column chromatography on silica gel eluting with a mixture of chloroform and methanol (20:1). The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford 6-[2-(hexylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone as yellow powder (50 mg).

mp: 90-92°C

IR(KBr): 3199, 1662, 1585 cm^{-1}

^1H NMR(DMSO-d_6,δ): 0.8-0.95(3H,m), 1.24(6H,d,J=6.6Hz), 1.15-1.4(6H,m), 1.45-1.65(2H,m), 3.15-3.35(2H,m), 5.10(1H, 7-plet,J=6.6Hz), 6.70(1H,d,J=9.7Hz), 6.87(1H,d,J=9.7Hz), 7.35-7.5(5H,m), 7.99(1H,t,J=5.5Hz)

APCI/MS: 397$[M+H]^+$, 419$[M+Na]^+$, 815$[2M+H]^+$

Elemental Analysis for $C_{22}H_{28}N_4OS \cdot 0.2H_2O$

Calcd.: C,66.04; H,7.15; N,14.00

Found : C,66.10; H,7.25; N,14.24

Example 15

2-Isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp: 234-236°C

IR(KBr): 3203, 1664, 1581 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.25(6H,d,J=6.6Hz), 2.87(3H,d,J=4.7Hz), 5.10(1H,7-plet,J=6.6Hz), 6.70(1H,d,J=9.7Hz), 6.86(1H,d,J=9.7Hz), 7.3-7.5(5H,m), 7.8-8.0(1H,m)

APCI/MS: 327$[M+H]^+$, 349$[M+Na]^+$

Elemental Analysis for $C_{17}H_{18}N_4OS \cdot 0.2H_2O$

Calcd.: C,61.87; H,5.62; N,16.98

Found : C,62.02; H,5.59; N,17.02

Example 16

2-Isopropyl-6-[4-phenyl-2-(3-pyridinylamino)-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp: 226-228°C

IR(KBr): 3045, 1660, 1581 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.27(6H,d), 5.13(1H,7-plet), 6.80(1H,d,J=9.7Hz), 7.01(1H,d,J=9.7Hz), 7.35-7.7(6H,m), 8.2-8.4(2H,m), 8.9-9.0(1H,m), 10.91(1H,brs)

APCI/MS: 390$[M+H]^+$, 412$[M+Na]^+$

Example 17

A mixture of 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone (150 mg) and N-methylthiourea (74.9 mg) in dioxane (1 ml) was stirred overnight at 80°C. The precipitate was collected by filtration to afford a yellow powder. The powder was recrystallized from ethanol to give 2-isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone hydrobromide as pale yellow crystals (95 mg).

mp: 226-228°C

IR(KBr): 3054, 1662, 1623, 1583 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.26(6H,d,J=3.3Hz), 2.98(3H,s), 5.10(1H, 7-plet,J=3.3Hz), 6.75(1H,d,J=8.4Hz), 6.78(1H,d,J=8.4Hz), 7.45-7.6(5H,m), 8.93(1H,br)

APCI/MS: 327$[M+H]^+$

Elemental Analysis for $C_{17}H_{18}N_4OS \cdot HBr$

Calcd.: C,49.91; H,4.73; N,13.69

Found : C,50.45; H,4.73; N,13.83

Example 18

6-(2-Anilino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone hydrobromide was obtained in a manner similar to Example 17.

mp: 127-129°C

IR(KBr): 3419, 1666, 1623, 1579 cm^{-1}

^{1}H NMR(DMSO-d_6,δ): 1.27(6H,d,J=3.3Hz), 5.11(1H,7-plet,J=3.3Hz), 6.76(1H,d,J=4.9Hz), 6.97(1H,d,J=4.9Hz), 6.9-7.05(1H,m), 7.3-7.4(2H,m), 7.4-7.5(3H,m), 7.5-7.6(2H,m), 7.6-7.7(2H,m), 10.46(1H,br)
APCI/MS: 389$[M+H]^+$
Elemental Analysis for $C_{22}H_{20}N_4OS \cdot HBr \cdot 1.4H_2O$
Calcd.: C,53.42; H,4.85; N,11.33
Found : C,53.40; H,4.79; N,11.21

Example 19

6-[2-(Butylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone hydrobromide was obtained in a manner similar to Example 17.
mp: 204-205°C
IR(KBr): 3415, 1668, 1633, 1585 cm^{-1}
^{1}H NMR(DMSO-d_6,δ): 0.91(3H,t,J=3.7Hz), 1.25(6H,d,J=3.3Hz), 1.3-1.45(2H,m), 1.5-1.65(2H,m), 5.10(1H,7-plet,J=3.3Hz), 6.72(1H,d,J=4.9Hz), 6.82(1H,d,J=4.9Hz), 7.4-7.55(5H,m), 8.55(1H,br)
APCI/MS: 369$[M+H]^+$
Elemental Analysis for $C_{20}H_{24}N_4OS \cdot HBr$
Calcd.: C,53.24; H,5.63; N,12.42
Found : C,53.64; H,5.60; N,12.50

Example 20

2-Isopropyl-6-{4-phenyl-2-[(2-pyridinylmethyl)amino]-1,3-thiazol-5-yl}-3(2H)-pyridazinone was obtained in a manner similar to Example 14.
mp: 182-184°C
IR(KBr): 3201, 1660, 1585 cm^{-1}
^{1}H NMR(DMSO-d_6,δ): 1.24(6H,d,J=6.6Hz), 4.61(2H,d,J=5.9Hz), 5.09(1H,7-plet,J=6.6Hz), 6.70(1H,d,J=9.6Hz), 6.88(1H,d, J=9.6Hz), 7.2-7.5(6H,m), 7.7-7.9(1H,m), 8.5-8.65(2H,m)
APCI/MS: 404$[M+H]^+$
Elemental Analysis for $C_{22}H_{21}N_5OS$
Calcd.: C,65.20; H,5.27; N,17.28

Found : C,65.18; H,5.25; N,17.33

Example 21

2-Isopropyl-6-(4-phenyl-2-{[2-(2-pyridinyl)ethyl]amino}-1,3-thiazol-5-yl)-3(2H)-pyridazinone hydrobromide was obtained in a manner similar to Example 17.

mp: 126-127°C

IR(KBr): 3205, 1660, 1581 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.24(6H,d,J=3.3Hz), 3.06(2H,t,J=3.6Hz), 3.66(2H,q,J=3.6Hz), 5.10(1H,7-plet,J=3.3Hz), 6.70(1H,d, J=4.9Hz), 6.87(1H,d,J=4.9Hz), 7.2-7.35(2H,m), 7.35-7.5(5H,m), 7.65-7.75(1H,m), 8.0-8.1(1H,m)

APCI/MS: 418$[M+H]^+$

Example 22

A mixture of 2-isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone hydrobromide (150 mg) and acetyl chloride (43.3 mg) in pyridine (3 ml) was stirred overnight at ambient temperature. The solvent was removed in vacuo to give an oil, which was subjected to a column chromatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford an oil, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-N-methylacetamide (60 mg).

mp: 165-167°C

IR(KBr): 1666, 1585 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.26(6H,d,J=6.6Hz), 2.43(3H,s), 3.69(3H,s), 5.13(1H,7-plet,J=6.6Hz), 6.81(1H,d,J=9.6Hz), 7.03(1H,d, J=9.6Hz), 7.35-7.6(5H,m)

APCI/MS: 369$[M+H]^+$

Elemental Analysis for $C_{19}H_{20}N_4O_2S$

Calcd.: C,61.64; H,5.50; N,15.13

Found : C,61.82; H,5.46; N,15.06

Example 23

A mixture of 2-isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone hydrobromide (100 mg), sodium hydride (61.3 mg) and methyl iodide (217mg) in dimethylformamide (4 ml) was stirred for 3 hours at ambient temperature. Water and ethyl acetate were added to the reaction mixture at ambient temperature. The separated organic layer was dried over sodium sulfate. The solvent was removed in vacuo to give a yellow powder, which was subjected to a column chromatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford 6-[2-(dimethylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)- pyridazinone as a yellow powder (44 mg).

mp: 158-160°C

IR(KBr): 1668, 1565 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.26(6H,d,J=6.6Hz), 3.10(6H,s), 5.10(1H, 7-plet,J=6.6Hz), 6.70(1H,d,J=9.8Hz), 6.85(1H,d,J=9.8Hz), 7.35-7.55(5H,m)

APCI/MS: 341$[M+H]^+$

Elemental Analysis for $C_{18}H_{20}N_4OS$

Calcd.: C,63.17; H,5.95; N,16.37

Found : C,62.89; H,5.88; N,16.15

Example 24

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (200 mg) and isoamyl nitrate (150 mg) in tetrahydrofuran (5 ml) was refluxed for 3 hours with stirring. The solvent was removed in vacuo to give a yellow oil, which was subjected to a column chromatography on silica gel eluting with a mixture of chloroform and methanol (20:1). The solvent was removed in vacuo to afford 2-isopropyl-6-(4-phenyl-1,3-thiazol-5-yl)- 3(2H)-pyridazinone as an oil.

IR(KBr): 1670, 1662, 1652, 1589 cm^{-1}

^1H NMR(DMSO-d_6,δ): 1.24(6H,d,J=6.6Hz), 5.13(1H,7-plet,J=6.6Hz), 6.86(1H,d,J=9.6Hz), 7.13(1H,d,J=9.6Hz), 7.4-7.6(5H,m), 9.23(1H,s)

APCI/MS: 298$[M+H]^+$

Example 25

Phenyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-ylcarbamate was obtained in a manner similar to Example 2.

mp : 205-207℃ (ethanol)

IR (KBr) : 3432, 1732, 1643 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.25(6H , d, J=6.6Hz), 5.12(1H, 7-plet, J=6.6 Hz), 6.79(1H, d, J=9.8 Hz), 6.99(1H, d, J=9.8Hz), 7.2-7.6(10H, m), 12.64(1H, br)

ESI/MS : 433$(M+1)^+$, 455$(M+Na)^+$

Example 26

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-pyridinecarboxamide was obtained in a manner similar to Example 2.

mp 245-246℃ (ethanol)

IR (KBr) : 3340, 1664, 1587 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.05(1H, d, J=9.7 Hz), 7.3-7.6(5H, m), 7.65-7.8(1H, m), 8.0-8.25(2H, m), 8.7-8.8(1H, m), 12.29(1H, brs)

ESI/MS : 418 $(M+H)^+$, 440 $(M+Na)^+$

Elemental Analysis for $C_{22}H_{19}N_5O_2S$

Calcd. C: 63.29, H: 4.59, N: 16.78

Found C: 63.25, H: 4.65, N: 16.73

Example 27

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-(4-morpholinylmethyl)benzamide was obtained in a manner similar to Example 2.

mp : 222-224℃ (diisopropyl ether)

IR (KBr) : 3442, 1648 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.3-2.45(4H, m), 3.5-3.7(6H, m), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.0-8.2(2H, m), 12.91(1H, br)

ESI/MS : 516$(M+H)^+$, 538 $(M+Na)^+$

Elemental Analysis for $C_{28}H_{29}N_5O_3S \cdot 0.3H_2O$

Calcd. C: 64.55, H: 5.73, N: 13.44

Found C: 64.72, H: 5.90, N: 12.97

Example 28

4-[(Dimethylamino)methyl]-N-[5-(1-isopropyl-6- oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.

mp : 246-248℃ (diisopropyl ether)

IR (KBr) : 3421, 1648 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.17(6H, s), 3.48(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.0-8.2(2H, m), 12.89(1H, br)

ESI/MS : 474$(M+H)^+$, 496$(M+Na)^+$

Elemental Analysis for $C_{26}H_{27}N_5O_2S \cdot 0.1H_2O$

Calcd. C: 65.69, H: 5.77, N: 14.73

Found C: 65.57, H: 5.73, N: 14.73

Example 29

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-methylpropanamide was obtained in a manner similar to Example 2.

mp : 231-232 ℃ (ethyl acetate)

IR (KBr) : 3181, 1689, 1648, 1581 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.14(6H, d, J=6.8Hz), 1.27(6H, d, J=6.6 Hz), 2.77(1H, 7-plet, J=6.8 Hz), 5.13(1H, 7-plet, J=6.6 Hz), 6.80(1H, d, J=9.6 Hz), 7.01(1H, d, J=9.6 Hz), 7.3-7.6(5H, m), 12.38(1H, brs)

ESI/MS : 383$(M+H)^+$, 405 $(M+Na)^+$

Elemental Analysis for $C_{20}H_{22}N_4O_2S$
Calcd. C: 62.81, H: 5.80, N: 14.65
Found C: 62.71, H: 5.77, N: 14.73

Example 30

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-naphthamide was obtained in a manner similar to Example 2.
mp : 227-229 ℃ (ethanol-ethyl acetate)
IR (KBr) : 3151, 1679, 1643, 1579 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.31(6H, d, J=6.6 Hz), 5.16(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.6 Hz), 7.06(1H, d, J=9.6 Hz), 7.3-7.8(7H, m), 7.9-8.2(4H, m), 8.85(1H, s), 13.10(1H, brs)
ESI/MS Nega : 465$(M-H)^+$
Elemental Analysis for $C_{27}H_{22}N_4O_2S$
Calcd. C: 69.51, H: 4.75, N: 12.01
Found C: 69.21, H: 4.91, N: 11.98

Example 31

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-1-naphthamide was obtained in a manner similar to Example 2.
mp : 223-224 ℃ (ethanol-ethyl acetate)
IR (KBr) : 3141, 1681, 1643, 1577 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.32(6H, d, J=6.6 Hz), 5.17(1H, 7-plet, J=6.6 Hz), 6.84(1H, d, J=9.6 Hz), 7.06(1H, d, J=9.6 Hz), 7.3-7.7(7H, m), 7.8-8.2(4H, m), 8.2-8.4(1H, m),, 13.10(1H, brs)
ESI/MS Nega : 465$(M-H)^+$
Elemental Analysis for $C_{27}H_{22}N_4O_2S \cdot 0.2H_2O$
Calcd. C: 68.98, H: 4.80, N: 11.92
Found C: 69.07, H: 4.73, N: 11.96

Example 32

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-

thiazol-2-yl]-4-morpholinecarboxamide was obtained in a manner similar to Example 2.

mp : 231-232 ℃ (ethyl acetate)

IR (KBr) : 3440, 1668 1590 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 3.4-3.7(8H, m), 5.12(1H, 7-plet, J=6.6 Hz), 6.77(1H, d, J=9.8 Hz), 6.96(1H, d, J=9.8 Hz), 7.3-7.6(5H, m), 11.25(1H, brs)

ESI/MS : 448$(M+Na)^+$

Elemental Analysis for $C_{21}H_{23}N_5O_3S$

Calcd. C: 59.28, H: 5.45 N: 16.45

Found C: 59.04, H: 5.49, N: 16.36

Example 33

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]cyclopropanecarboxamide was obtained in a manner similar to Example 2.

mp : 226-227 ℃ (ethyl acetate)

IR (KBr) : 3392, 1687 1639 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 0.8-1.0(4H, m), 1.26(6H, d, J=6.6 Hz), 1.85-2.05(1H, m), 5.13(1H, 7-plet, J=6.6 Hz), 6.80(1H, d, J=9.8 Hz), 7.01(1H, d, J=9.8 Hz), 7.3-7.6(5H, m), 12.69(1H, brs)

ESI/MS : 381$(M+H)^+$, 403$(M+Na)^+$

Elemental Analysis for $C_{20}H_{20}N_4O_2S \cdot 0.2H_2O$

Calcd. C: 62.55, H: 5.35, N: 14.59

Found C: 62.50, H: 5.30, N: 14.60

Example 34

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-methylbenzamide was obtained in a manner similar to Example 2.

mp : 221-222 ℃ (ethyl acetate)

IR (KBr) : 3135, 1681 1641 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 2.44(3H, s), 5.13(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8 Hz),

7.2-7.7(9H, m), 12.81(1H, brs)
ESI/MS : 431(M+H)$^+$, 453(M+Na)$^+$
Elemental Analysis for $C_{24}H_{22}N_4O_2S$
Calcd. C: 66.96, H: 5.15, N: 13.01
Found C: 67.11, H: 5.22, N: 13.04

Example 35

3-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.
mp : 173-174 ℃ (ethanol)
IR (KBr) : 3426, 1649, 1579 cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7 Hz), 7.4-7.8(7H, m), 8.0-8.1(1H, m), 8.15-8.25(1H, m), 13.07(1H, brs)
ESI/MS Nega : 449(M-H)$^+$
Elemental Analysis for $C_{23}H_{19}ClN_4O_2S$
Calcd. C: 61.26, H: 4.25, N: 12.43
Found C: 61.03, H: 4.04, N: 12.55

Example 36

3-Fluoro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.
mp : 183-184 ℃ (ethanol)
IR (KBr) : 3421, 1639, 1575 cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7 Hz), 7.4-7.7(7H, m), 7.9-8.1(2H, m), 13.05(1H, brs)
ESI/MS : 435(M+H)$^+$, 457(M+Na)$^+$
Elemental Analysis for $C_{23}H_{19}FN_4O_2S$
Calcd. C: 63.58, H: 4.41, N: 12.89
Found C: 63.49, H: 4.40, N: 12.94

Example 37

2-Fluoro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.

mp : 251-252 ℃ (ethanol-ethyl acetate)

IR (KBr) : 3421, 1666, 1587 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7 Hz), 7.2-7.9(9H, m), 12.91(1H, brs)

ESI/MS : 435$(M+H)^+$, 457$(M+Na)^+$

Calcd. C: 63.58, H: 4.41, N: 12.89

Found C: 63.39, H: 4.70, N: 12.89

Example 38

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-(trifluoromethyl)benzamide was obtained in a manner similar to Example 2.

mp : 237-238 ℃ (ethanol)

IR (KBr) : 1646, 1581 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.6 Hz), 7.04(1H, d, J=9.6 Hz), 7.35-7.6(5H, m), 7.80(1H, t, J=8Hz), 8.02(1H, t, J=8Hz), 8.42(1H, t, J=8Hz), 8.53(1H, s), 13.23(1H, brs)

ESI/MS : 485$(M+H)^+$, 507$(M+Na)^+$

Elemental Analysis for $C_{24}H_{19}F_3N_4O_2S$

Calcd. C: 59.50, H: 3.95, N: 11.56

Found C: 59.476, H: 3.97, N: 11.54

Example 39

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-(trifluoromethyl)benzamide was obtained in a manner similar to Example 2.

mp 162-167 ℃ (ethanol)

IR (KBr) : 1648, 1579 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.6 Hz), 7.04(1H, d, J=9.6 Hz), 7.3-7.6(5H, m), 7.95(2H, d, J=8.4Hz), 8.32(2H, t, J=8.4Hz), 13.22(1H, brs)

ESI/MS : 485$(M+H)^+$, 507$(M+Na)^+$

Elemental Analysis for $C_{24}H_{19}F_3N_4O_2S \cdot 0.1H_2O$

Calcd. C: 59.50, H: 3.95 N: 11.56

Found C: 59.28, H: 3.98, N: 11.52

Example 40

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(trifluoromethyl)benzamide was obtained in a manner similar to Example 2.

mp : 219-220 ℃ (ethanol)

IR (KBr) : 3174, 1650, 1583 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.29 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.6 Hz), 7.04(1H, d, J=9.6 Hz), 7.3-7.6(5H, m), 7.7-7.95(4H, m), 13.13(1H, brs)

ESI/MSnega : 483$(M-H)^+$

Elemental Analysis for $C_{24}H_{19}F_3N_4O_2S$

Calcd. C: 59.50, H: 3.95, N: 11.56

Found C: 59.44, H: 4.03, N: 11.70

Example 41

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-methoxybenzamide was obtained in a manner similar to Example 2.

mp : >250 ℃ (ethanol)

IR (KBr) : 3315, 1658, 1585 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 3.93(3H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.6 Hz), 6.9-7.25(3H, m), 7.4-7.65(6H, m), 7.65-7.8(1H, m), 12.09(1H, brs)

ESI/MS : 447$(M+H)^+$, 469$(M+Na)^+$

Elemental Analysis for $C_{24}H_{22}O_3S$

Calcd. C: 64.56, H: 4.97, N: 12.55

Found C: 64.56, H: 4.96, N: 12.60

Example 42

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-methylbenzamide was obtained in a manner similar to Example 2.

mp : 198-199 ℃(ethyl acetate)

IR (KBr) : 3349, 1646, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 2.40(3H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8Hz), 7.3-7.6(7H, m), 7.8-8.05(2H, m), 12.88(1H, brs)

ESI/MS : 431$(M+H)^+$, 453$(M+Na)^+$

Elemental Analysis for $C_{24}H_{22}O_2S \cdot 0.2H_2O$

Calcd. C: 66.40, H: 5.20, N: 12.91

Found C: 66.50, H: 5.32, N: 12.73

Example 43

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-methylbenzamide was obtained in a manner similar to Example 2.

mp : 198-199 ℃ (ethyl acetate)

IR (KBr) : 3388, 1660, 1581 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 2.40(3H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.8 Hz), 7.03(1H, d, J=9.8Hz), 7.3-7.6(7H, m), 8.05(1H, d, J=8.2Hz), 12.87(1H, brs)

ESI/MS : 431$(M+H)^+$, 453$(M+Na)^+$

Elemental Analysis for $C_{24}H_{22}O_2S \cdot 0.2H_2O$

Calcd. C: 66.40, H: 5.20 N: 12.91

Found C: 66.50, H: 5.32, N: 12.73

Example 44

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3,5-bis(trifluoromethyl)benzamide was obtained in a manner similar to Example 2.

mp : 207-208 ℃ (ethanol)

IR (KBr) : 1646, 1575 m^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.6 Hz), 7.05(1H, d, J=9.6Hz), 7.3-7.6(5H, m), 8.43(1H, s), 8.79(2H, s), 13.44(1H, brs)

ESI/MSNega : 551$(M-H)^+$

Elemental Analysis for $C_{25}H_{18}N_4O_2S$

Calcd. C: 54.35, H: 3.28, N: 10.14

Found C: 54.41, H: 3.30, N: 10.36

Example 45

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-methoxybenzamide was obtained in a manner similar to Example 2.

mp : 219-221 ℃ (ethanol)

IR (KBr) : 3421, 1646, 1577 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 3.86(3H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.6 Hz), 6.95-7.15(3H, m), 7.35-7.65(5H, m), 8.05-8.2(2H, m)

ESI/MS : 447$(M+H)^+$, 469$(M+Na)^+$

Elemental Analysis for $C_{25}H_{18}N_4O_2S$

Calcd. C: 64.30, H: 4.99, N: 12.50

Found C: 64.17, H: 4.93, N: 12.80

Example 46

2-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.

mp : 220-221 ℃ (ethanol)

IR (KBr) : 3421, 1641, 1573 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8Hz), 7.3-7.7(9H, m), 13.03(1H, brs)

ESI/MS : 473$(M+Na)^+$

Elemental Analysis for $C_{23}H_{19}ClN_4O_2S$
Calcd. C: 61.26, H: 4.25, N: 12.42
Found C: 61.16, H: 4.22, N: 12.38

Example 47

4-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.
mp : 205-206 ℃ (ethanol)
IR (KBr) : 3178, 1641, 1575 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8Hz), 7.3-7.7(7H, m), 8.15(2H, dd, J=2Hz and 9.1Hz), 13.04(1H, brs)
ESI/MS Nega: 449$(M-H)^+$
Elemental Analysis for $C_{23}H_{19}ClN_4O_2S$
Calcd. C: 61.26, H: 4.25, N: 12.42
Found C: 61.27, H: 4.26, N: 12.41

Example 48

4-fluoro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.
mp : 225-226 ℃ (ethanol)
IR (KBr) : 3180, 1679, 1641, 1575 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.30 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8Hz), 7.3-7.6(7H, m), 8.1-8.3(2H, m), 12.98(1H, brs)
ESI/MS : 435$(M+H)^+$, 457$(M+Na)^+$
Elemental Analysis for $C_{23}H_{19}FN_4O_2S$
Calcd. C: 63.58, H: 4.41, N: 12.89
Found C: 63.57, H: 4.44, N: 12.94

Example 49

2,6-Dichloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-

4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.

mp : 248-249 ℃ (ethyl acetate)

IR (KBr) : 3428, 1679, 1646, 1581 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.29 (6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7Hz), 7.05(1H, d, J=9.7Hz), 7.3-7.7(8H, m), 13.28(1H, brs)

ESI/MS : 485$(M)^+$

Example 50

N'-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-N,N-dimethylurea was obtained in a manner similar to Example 2.

mp : 199-200 ℃ (ethyl acetate)

IR (KBr) : 3239, 1673, 1648, 1583 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6Hz), 2.98(6H, s), 5.13(1H, 7-plet, J=6.6 Hz), 6.77(1H, d, J=9.6 Hz), 6.96(1H, d, J=9.6 Hz), 7.3-7.6(5H, m), 11.03(1H, brs)

ESI/MS : 384$(M+H)^+$, 406 $(M+Na)^+$

Example 51

4-Iodo-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.

mp : 253-254 ℃ (ethanol)

IR (KBr) :1673, 1643, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.29(6H, d, J=6.6Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7z), 7.04(1H, d, J=9.7 Hz), 7.3-7.6(5H, m), 7.8-8.0(4H, m), 13.02(1H, br)

ESI/MS : 543$(M+H)^+$, 565 $(M+Na)^+$

Example 52

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-1-piperidinecarboxamide was obtained in a manner similar

to Example 2.

mp : 138-140 ℃ (ethyl acetate-isopropyl ether)

IR (KBr) : 3224, 1652, 1581 cm^{-1}

ESI/MS : 424$(M+H)^+$, 446 $(M+Na)^+$

Example 53

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(trifluoromethoxy)benzamide was obtained in a manner similar to Example 2.

mp : 212-213 ℃ (ethanol)

IR (KBr) : 3141, 1646, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6Hz), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7z), 7.04(1H, d, J=9.7 Hz), 7.3-7.8(7H, m), 8.0-8.25(2H, m), 13.18(1H, br)

ESI/MS Nega: 499$(M-H)^-$

Example 54

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-9H-carbazole-9-carboxamide was obtained in a manner similar to Example 2.

mp : 241-242 ℃ (ethanol)

IR (KBr) : 3089, 1652, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.2-1.4 (6H, m), 5.15(1H, 7-plet, J=6.6 Hz), 6.79(1H, d, J=9.7z), 6.87(1H, d, J=9.7 Hz), 7.3-7.7(10H, m), 8.0-8.2(2H, m), 8.7-9.0(2H, br)

ESI/MS : 504 $(M+H)^+$

Example 55

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]isonicotinamide was obtained in a manner similar to Example 2.

mp : 223-224 ℃ (ethanol)

IR (KBr) :3432, 1668, 1583 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6Hz), 5.15(1H, 7-plet, J=6.6

Hz), 6.83(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8 Hz), 7.35-7.6(5H, m), 8.03(2H, dd, J=1.4 and 4.6Hz), 8.83(2H, dd, J=1.4 and 4.6Hz), 13.28(1H, brs)

ESI/MS : 418 $(M+H)^+$, 440 $(M+Na)^+$

Example 56

4-(Chloromethyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 2.

mp : >250 ℃ (ethanol)

IR (KBr) :3419, 1650, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6Hz), 4.86(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.8 Hz), 7.04(1H, d, J=9.8 Hz), 7.3-7.7(7H, m), 8.0-8.2(2H, m), 12.99(1H, brs)

ESI/MS : 465 $(M+H)^+$, 487 $(M+Na)^+$

Example 57

N-[4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazol-2-yl]cyclopropanecarboxamide was obtained in a manner similar to Example 2.

mp : 250-252 ℃ (ethanol)

IR (KBr) : 3154, 1689, 1646, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 0.8-1.0(4H, m), 1.25(6H, d, J=6.6Hz), 1.9-2.1(1H, m), 5.12(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.6z), 7.04(1H, d, J=9.6 Hz), 7.2-7.35(25H, m), 7.5-7.6(2H, m), 12.72(1H, br)

ESI/MS : 399$(M+H)^+$, 421$(M+Na)^+$

Example 58

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-methylbutanamide was obtained in a manner similar to Example 2.

mp : 198-199℃ (ethyl acetate-isopropyl ether)

mp : >250 ℃(diisopropyl ether)

IR (KBr) :3154, 1689, 1646, 1579 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 0.94(6H, d, J =6.6Hz), 1.28(6H, d, J =6.6Hz), 2.11(1H, m), 2.36(2H, d, J =7.1Hz), 5.14(1H, 7-plet, J=6.6 Hz), 6.80(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7 Hz), 7.35-7.6(5H, m), 12.39(1H, brs)
ESI/MS : 397 $(M+H)^+$, 419 $(M+Na)^+$

Example 59

2-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-(4-fluorophenyl)-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 2.

^{1}H NMR ($CDCl_3$, δ) : 1.40(6H, d, J=6.6 Hz), 4.24(2H, s), 5.32(1H, 7-plet, J=6.6 Hz), 6.76(1H, d, J=9.6 Hz), 6.94(1H, d, J=9.6 Hz), 7.0-7.2(2H, m), 7.4-7.6(2H, m), 10.13(1H, br)
ESI/MS : 429$(M+Na)^+$
Elemental Analysis for $C_{22}H_{19}N_5O_2S$
Calcd. C: 63.29, H: 4.59, N: 16.78
Found C: 63.25, H: 4.65, N: 16.73

Example 60

2-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 2.

^{1}H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 4.44(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.03(1H, d, J=9.6 Hz), 7.3-7.6(5H, m), 12.81(1H, br)
ESI/MS : 389$(M+H)^+$, 411$(M+Na)^+$

Example 61

6-[2-(tert-Butylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 189-190℃ (ethanol)
IR (KBr) : 3288, 3257, 1648, 1581 cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 1.23(6H, d, J=6.6 Hz), 1.40(9H, s), 5.10(1H, 7-plet, J=6.6 Hz), 6.72(1H, d, J=9.7 Hz), 6.94(1H, d, J=9.7 Hz), 7.3-7.55(5H, m), 7.72(1H, s)

ESI/MS : 369(M+H)$^+$, 391(M+Na)$^+$

Elemental Analysis for $C_{20}H_{24}N_4OS$

Calcd. C: 65.19; H:6.56 ; N: 15.20

Found C: 65.12; H: 6.59; N: 15.20

Example 62

6-[2-(Ethylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 167-169℃ (ethanol)

IR (KBr) : 3203, 1664, 1575 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.18(3H, t, J=7.3 Hz), 1.25(6H, d, J=6.7Hz), 3.15-3.4(2H, m), 5.10(1H, 7-plet, J=6.7 Hz), 6.70(1H, d, J=9.6 Hz), 6.87(1H, d, J=9.6 Hz), 7.3-7.55(5H, m), 7.97(1H, t, J=5.3Hz)

ESI/MS : 341(M+H)$^+$, 363 (M+Na)$^+$

Elemental Analysis for $C_{18}H_{20}N_4OS \cdot 0.2H_2O$

Calcd. C: 62.84, H: 5.98, N: 16.28

Found C: 62.85, H: 5.97, N: 16.31

Example 63

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]guanidine was obtained in a manner similar to Example 14.

mp : >250℃ (ethanol)

IR (KBr) : 3405, 1656 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.22(6H, t, J=6.6 Hz), 5.09(1H, 7-plet, J=6.6 Hz), 6.72(1H, d, J=9.6 Hz), 6.93(1H, d, J=9.6 Hz), 6.9-7.1(4H, br), 7.3-7.55(5H, m)

ESI/MS : 355(M+H)$^+$, 377 (M+Na)$^+$

Elemental Analysis for $C_{17}H_{18}N_6OS \cdot 0.2H_2O$

Calcd. C: 57.03, H: 5.18, N: 23.47

Found C: 56.99, H: 5.22, N: 23.29

Example 64

2-Isopropyl-6-[2-(isopropylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp 138-139℃ (ethanol)

IR (KBr) : 3259, 1650, 1585 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.0-1.3(12H, m), 3.7-3.95(1H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.6 Hz), 6.87(1H, d, J=9.6 Hz), 7.3-7.6(4H, m), 7.8-8.0(1H, m)

ESI/MS : 355$(M+H)^+$, 377 $(M+Na)^+$

Example 65

6-[2-(Benzylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp 157-158℃ (ethanol)

IR (KBr) : 3201, 1662, 1583 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.23(6H, d, J=6.6Hz), 4.52(2H, d, J=5.9Hz), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.7 Hz), 6.88(1H, d, J=9.7 Hz), 7.1-7.6(10H, m), 8.50(1H, t, J=5.9Hz)

ESI/MS : 403$(M+H)^+$, 425 $(M+Na)^+$

Example 66

6-{2-[(2-Furylmethyl)amino]-4-phenyl-1,3-thiazol-5-yl}-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 115-116℃ (ethanol)

IR (KBr) : 3201, 1658, 1583 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.6Hz), 4.50(2H, d, J=5.6Hz), 5.10(1H, 7-plet, J=6.6 Hz), 6.3-6.45(2H, m), 6.71(1H, d, J=9.7 Hz), 6.89(1H, d, J=9.7 Hz), 7.3-7.7(6H, m), 8.40(1H, t, J=5.6Hz)

ESI/MS : 393$(M+H)^+$, 415 $(M+Na)^+$

Example 67

2-Isopropyl-6-[4-phenyl-2-(2-pyridinylamino)-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 194-195℃ (ethanol)

IR (KBr) : 3444, 1646, 1577 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.29(6H, d, J=6.6Hz), 5.14(1H, 7-plet, J=6.6 Hz), 6.78(1H, d, J=9.7 Hz), 6.9-7.15(3H, m), 7.3-7.7(5H, m), 7.6-7.8(1H,

m), 8.25-8.4(1H, m), 11.6(1H, br)
ESI/MS : 390$(M+H)^+$, 412 $(M+Na)^+$

Example 68

2-Isopropyl-6-(2-{[3-(4-morpholinyl)propyl]amino}-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone was obtained in a manner similar to Example 14.
mp : 194-195℃ (ethanol)
IR (KBr) : 3444, 1646, 1577 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.25(6H, d, J=6.6Hz), 1.6-1.85(2H, m), 2.2-2.45(6H, m), 3.2-3.4(2H, m), 3.5-3.7(4H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.8 Hz), 6.87(1H, d, J=9.8Hz), 7.3-7.6(5H, m), 8.01(1H, t, J=5.5Hz)
ESI/MS : 440$(M+H)^+$, 462 $(M+Na)^+$

Example 69

2-Isopropyl-6-(2-{[2-(4-morpholinyl)ethyl]amino}-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone was obtained in a manner similar to Example 14.
IR (KBr) : 3444, 1646, 1577 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.6Hz), 2.3-2.6(6H, m), 3.2-3.7(6H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.6 Hz), 6.87(1H, d, J=9.6Hz), 7.3-7.6(5H, m), 7.85-8.0(1H, m)
ESI/MS : 426$(M+H)^+$, 448 $(M+Na)^+$

Example 70

6-[2-(Cyclohexylamino)-4-phenyl-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 14.
mp : 149-151℃ (ethanol)
IR (KBr) : 3203, 1668, 1569 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.6Hz), 1.1-1.4(5H, m), 1.45-1.8(3H, m), 1.85-2.05(2H, m), 3.4-3.6(1H, br), 5.10(1H, 7-plet, J=6.6 Hz), 6.69(1H, d, J=9.8 Hz), 6.87(1H, d, J=9.8Hz), 7.3-7.55(5H, m), 7.94(1H, d, J=7.6Hz)

ESI/MS : 395 $(M+H)^+$, 417 $(M+Na)^+$

Example 71

2-Isopropyl-6-{2-[(2-methoxyethyl)amino]-4-phenyl-1,3-thiazol-5-yl}-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 112-114℃ (isopropyl ether)

IR (KBr) : 3363, 1664, 1587 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.6Hz), 3.29(3H, s), 3.35-3.6(4H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.6 Hz), 6.87(1H, d, J=9.6Hz), 7.3-7.55(5H, m), 8.0-8.2(1H, m)

ESI/MS : 371 $(M+H)^+$, 393 $(M+Na)^+$

Example 72

2-Isopropyl-6-[2-(1-naphthylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 239-240℃ (ethanol)

IR (KBr) : 1664, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.6Hz), 5.10(1H, 7-plet, J=6.6 Hz), 6.76(1H, d, J=9.7 Hz), 6.96(1H, d, J=9.7Hz), 7.3-7.8(9H, m), 7.85-8.3(3H, m), 10.38(1H, br)

ESI/MS : 439 $(M+H)^+$, 461 $(M+Na)^+$

Example 73

2-Isopropyl-6-[4-phenyl-2-(propylamino)-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 165-166℃ (ethanol)

IR (KBr) : 3205, 1666, 1577 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 0.92(3H, t, J=7.4Hz), 1.24(6H, d, J=6.6Hz), 1.59(2H, m), 3.1-3.4(2H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.7 Hz), 6.87(1H, d, J=9.7Hz), 7.3-7.55(5H, m), 8.01(1H, t, J=5.4Hz)

ESI/MS : 355 $(M+H)^+$, 377 $(M+Na)^+$

Example 74

2-Isopropyl-6-(4-phenyl-2-{[2-(1-piperidinyl)ethyl]amino}-1,3-

thiazol-5-yl)-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 165-166 ℃ (isopropyl ether)

IR (KBr) : 3205, 1666, 1577 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.6Hz), 1.3-1.6(6H, m), 2.3-2.6(4H, m), 3.2-3.5(4H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.70(1H, d, J=9.8 Hz), 6.87(1H, d, J=9.7Hz), 7.3-7.55(5H, m), 7.8-7.9(1H,m)

ESI/MS : 424 $(M+H)^+$

Example 75

6-(2-{[4-(Dimethylamino)phenyl]amino}-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 14.

mp : 234-236℃ (ethanol)

^1H NMR (DMSO-d_6, δ) : 1.25(6H, d, J=6.6 Hz), 2.85(3H,s), 5.10(1H, 7-plet, J=6.6 Hz), 6.6-6.8(3H, m), 6.93(1H, d, J=9.7 Hz), 7.3-7.6(7H, m), 10.07(1H, brs)

ESI/MS : 432$(M+H)^+$, 454 $(M+Na)^+$

Elemental Analysis for $C_{24}H_{25}N_5OS$

Calcd. C: 66.80, H: 5.84, N: 16.23

Found C: 66.90, H: 5.87 N: 16.32

Example 76

A solution of 6-[1-chloro-2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone (300 mg) and thiourea (88.8 mg) in dimethylformamide (0.6 mL) was heated for 35 hours at 80-85 ℃. After cooling, a mixture of a saturated sodium hydrogencarbonate (1.5 mL) and water (5 mL) was added to the reaction mixture and the resalting mixture was stirred for one hour. The precipitates were collected by filtration and dried over phosphorus petoxide under reduced pressure to give 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazol-2-ylformamide as a solid (324 mg).

m.p.: 230-231℃ (ethanol)

IR (KBr) : 1736, 1668, 1587 cm^{-1}

APCI/MS : 358$(M+H)^+$, 331

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.62 Hz), 5.31(1H, 7-plet, J=6.62 Hz), 6.72(1H, d, J=9.67 Hz), 6.85(1H, d, J=9.67 Hz), 7.13-7.26(2H, m), 7.46-7.57(2H, m), 7.68(1H, s), 12.08(1H, s)

Elemental Analysis for $C_{17}H_{15}FN_4O_2S$

Calcd. C: 56.97; H: 4.22; N: 15.63

Found C: 57.01; H: 4.26; N: 15.68

Example 77

A solution of 6-[1-chloro-2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone (300 mg) and thiourea (88.8 mg) in dioxane (0.6 mL) was heated for 20 hours at 80-85 ℃. After cooling, a mixture of a saturated sodium hydrogencarbonate (1.5 mL) and water (5 mL) was added to the reaction mixture and the resulting mixture was stirred for one hour. The precipitates were collected by filtration and dried over phosphorus petoxide under reduced pressure to give 6-[2-amino-4-(4-fluorophenyl)-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (301mg).

m.p.: 255.5-257℃ (ethanol)

IR (KBr) : 3384, 1650, 1582, 1523 cm^{-1}

ESI/MS : 353$(M+Na)^+$, 331$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 1.23(6H, d, J=6.60 Hz), 5.09(1H, 7-plet, J=6.60 Hz), 6.73(1H, d, J=9.70 Hz), 6.92(1H, d, J=9.70 Hz), 7.18-7.27(2H, m), 7.41(2H, s), 7.44-7.54(2H, m)

Elemental Analysis for $C_{16}H_{15}FN_4OS$

Calcd. C: 58.17; H: 4.58; N: 16.96

Found C: 58.42; H: 4.65; N: 17.05

Example 78

N-[4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazol-2-yl]-benzamide was obtained in a manner similar to Example 77.

m.p.: 228-230℃ (ethanol - n-hexane)

IR (KBr) : 3224, 1648, 1579, 1529 cm^{-1}

ESI/MS : 891($2M+Na)^+$, 457($M+Na)^+$, 435($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.41(6H, d, J=6.64 Hz), 5.33(1H, 7-plet, J=6.64 Hz), 6.72(1H, d, J=9.71 Hz), 6.95(1H, d, J=9.71 Hz), 7.05-7.15(2H, m), 7.45-7.64(5H, m), 7.91-7.97(2H, m), 9.87(1H, br.s)

Elemental Analysis for $C_{23}H_{19}FN_4O_2S$

Calcd. C: 63.58; H: 4.41; N: 12.89

Found C: 63.62; H: 4.39; N: 12.89

Example 79

6-[2-Amino-4-(2-fluorophenyl)-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 77.

m.p.: 233-235℃ (ethanol)

IR (KBr) : 3361, 3280, 3130, 1655, 1587, 1523 cm^{-1}

ESI/MS : 683($2M+Na)^+$, 353($M+Na)^+$, 331($M+H)^+$

^1H NMR (DMSO-d_6, δ) : 1.17(6H, d, J=6.60 Hz), 5.06(1H, 7-plet, J=6.60 Hz), 6.75(1H, d, J=9.90 Hz), 6.88(1H, d, J=9.90 Hz), 7.21-7.32(2H, m), 7.42-7.55(4H, m)

Elemental Analysis for $C_{16}H_{15}FN_4OS$

Calcd. C: 58.17; H: 4.58; N: 16.96

Found C: 58.06; H: 4.79; N: 16.61

Example 80

6-[2-Amino-4-(3-fluorophenyl)-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 77.

m.p.: 237-238℃ (ethanol)

IR (KBr) : 3384, 3294, 3134, 1653, 1635, 1581, 1522 cm^{-1}

ESI/MS : 683($2M+Na)^+$, 353($M+Na)^+$, 331($M+H)^+$

^1H NMR (DMSO-d_6, δ) : 1.23(6H, d, J=6.62 Hz), 5.10(1H, 7-plet, J=6.62 Hz), 6.76(1H, d, J=9.62 Hz), 6.97(1H, d, J=9.62 Hz), 7.21-7.32(3H, m), 7.38-7.50(3H, m)

Elemental Analysis for $C_{16}H_{15}FN_4OS$

Calcd. C: 58.17; H: 4.58; N: 16.96

Found C: 58.19; H: 4.62; N: 16.95

Example 81

6-[2-Amino-4-(3-chlorophenyl)-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 77.

m.p.: 235.5-237℃ (ethanol)

IR (KBr) : 3334, 3296, 3091, 1647, 1576, 1533 cm^{-1}

ESI/MS : 371 and 369$(M+Na)^+$, 349 and 347$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 1.22(6H, d, J=6.62 Hz), 5.10(1H, 7-plet, J=6.62 Hz), 6.77(1H, d, J=9.60 Hz), 7.00(1H, d, J=9.60 Hz), 7.38-7.52(6H, m)

Elemental Analysis for $C_{16}H_{15}ClN_4OS$

Calcd. C: 55.41; H: 4.36; N: 16.15

Found C: 55.48; H: 4.43; N: 16.10

Example 82

Acetyl chloride (0.855 mL) was added to a solution of 6-[2-amino-4-(4-fluorophenyl)-1,3-thiazol-5-yl]-2-isopropyl-3(2H)-pyridazinone (331 mg) in pyridine (6 mL) at ambient temperature and stirred at the same temperature for 2 hours. Pyridine was removed under reduced pressure to give a syrup. The syrup was dissolved in chloroform, washed with 1N-hydrochloric acid, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol - dichloromethane 2 : 98 v/v) to give N-[4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazol-2-yl]acetamide as a solid (273 mg).

m.p.: 236-237.5℃ (ethanol)

IR (KBr) : 1649, 1577, 1550 cm^{-1}

ESI/MS : 767$(2M+Na)^+$, 395$(M+Na)^+$, 373$(M+H)^+$

1H NMR (DMSO-d_6, δ) : 1.26(6H, d, J=6.64 Hz), 2.19(3H, s), 5.13(1H, 7-plet, J=6.64 Hz), 6.82(1H, d, J=9.70 Hz), 7.06(1H, d, J=9.70 Hz), 7.21-7.32(2H, m), 7.50-7.59(2H, m), 12.42(1H, br.s)

Elemental Analysis for $C_{18}H_{17}FN_4OS$

Calcd. C: 58.05; H: 4.60; N: 15.04

Found C: 58.07; H: 4.61; N: 14.98

Example 83

N-[4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazol-2-yl]-benzamide was obtained in a manner similar to Example 82.

m.p.: 202-203.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3234, 3187, 1670, 1583, 1549 cm^{-1}

ESI/MS : 457$(M+Na)^+$, 435$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.42(6H, d, J=6.58 Hz), 5.33(1H, 7-plet, J=6.58 Hz), 6.73(1H, d, J=9.70 Hz), 6.91(1H, d, J=9.70 Hz), 7.12-7.21(2H, m), 7.46-7.63(5H, m), 8.05-8.18(3H, m)

Elemental Analysis for $C_{23}H_{19}FN_4O_2S$

Calcd. C: 63.58; H: 4.41; N: 12.89

Found C: 63.62; H: 4.39; N: 12.89

Example 84

A mixture of 6-(1-bromo-2-oxo-2-phenylethyl)-3(2H)-pyridazinone (1.00 g) and thiourea (311 mg) in 1-methyl-2-pyrrolidinone (2 mL) was heated for 6 hours at 80-85℃. The mixture was poured into a saturated sodium hydrogencarbonate solution (3 mL) and the mixture was stirred for one hour to give a solid. The solid was collected by filtration, dried over phosphorous pentoxide and triturated with diisopropyl ether to give 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone as a solid (0.84 g).

m.p.: >250℃ (ethanol)

IR (KBr) : 3311, 3151, 1668, 1647, 1593, 1547, 1510 cm^{-1}

ESI/MS : 563$(2M+Na)^+$, 293$(M+Na)^+$, 271$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 6.66(1H, dd, J=1.59,9.98 Hz), 6.86(1H, d, J=9.98 Hz), 7.37-7.49(7H, m), 12.93(1H, br.s)

Elemental Analysis for $C_{13}H_{10}N_4OS$

Calcd. C: 57.76; H: 3.73; N: 20.73

Found C: 57.48; H: 3.66; N: 20.55

Example 85

To a solution of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone (1010 mg) in dimethylformamide (10 mL) was added sodium hydride (60 % in oil) (157 mg), and the mixture was stirred for 30 minutes at 50-55℃. Iodomethane (0.279 mL) was added to the mixture and the resulting mixture was stirred for 8 hours at 50-55℃. The mixture was poured into water (100 mL) to give a solid. The solid was collected by filtration, dried over phosphorous pentoxide and purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 60 : 40 and then 20 : 80, v/v) to give 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-methyl-3(2H)-pyridazinone as a solid (185 mg).

m.p.: 238-241℃ (ethanol - diisopropyl ether)

IR (KBr) : 3344, 3122, 1657, 1581, 1522 cm^{-1}

ESI/MS : 591$(2M+Na)^+$, 307$(M+Na)^+$, 285$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 3.62(3H, s), 6.72(1H, d, J=9.76 Hz), 6.86(1H, d, J=9.76 Hz), 7.37-7.47(7H, m)

Elemental Analysis for $C_{14}H_{12}N_4OS$

Calcd. C: 59.14; H: 4.25; N: 19.70

Found C: 58.95; H: 4.18; N: 19.54

Example 86

6-(2-Amino-4-phenyl-1,3-thiazol-5-yl)-2-propyl-3(2H)-pyridazinone was obtained in a manner similar to Example 85.

m.p.: 224-226℃ (ethanol)

IR (KBr) : 3444, 3280, 1649, 1579, 1535 cm^{-1}

ESI/MS : 647$(2M+Na)^+$, 335$(M+Na)^+$, 313$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 0.88(3H, t, J=7.38 Hz), 1.65-1.75(2H, m), 3.97 (2H, t, J=7.08Hz), 6.72(1H, d, J=9.72 Hz), 6.88(1H, d, J=9.72 Hz), 7.38-7.47(7H, m)

Elemental Analysis for $C_{15}H_{14}N_4OS \cdot 0.1H_2O$

Calcd. C: 61.17; H: 5.20; N: 17.83

Found C: 61.21; H: 5.11; N: 17.69

Example 87

6-(2-Amino-4-phenyl-1,3-thiazol-5-yl)-2-(2-methoxyethyl)-3(2H)-pyridazinone was obtained in a manner similar to Example 85.

m.p.: 208-209.5℃ (ethanol)

IR (KBr) : 3361, 3097, 1668, 1589, 1522 cm^{-1}

ESI/MS : 679$(2M+Na)^+$, 351$(M+Na)^+$, 329$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 3.25(3H, s), 3.67(2H, t, J=5.64 Hz), 4.18(2H, t, J=5.64 Hz), 6.73(1H, d, J=9.75 Hz), 6.87(1H, d, J=9.75 Hz), 7.39-7.47(7H, m)

Elemental Analysis for $C_{16}H_{16}N_4O_2S \cdot 0.2H_2O$

Calcd. C: 57.89; H: 4.98; N: 16.88

Found C: 57.87; H: 4.81; N: 16.90

Example 88

6-(2-Amino-4-phenyl-1,3-thiazol-5-yl)-2-(cyclopropylmethyl)-3(2H)-pyridazinone was obtained in a manner similar to Example 85.

m.p.: 204-206℃ (ethanol - diisopropyl ether)

IR (KBr) : 3354, 3132, 1653, 1581, 1520 cm^{-1}

ESI/MS : 671$(2M+Na)^+$, 347$(M+Na)^+$, 325$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 0.34-0.39(2H, m), 0.46-0.52(2H, m), 1.19-1.23(1H, m), 3.87(2H, d, J=7.16 Hz), 6.73(1H, d, J=9.74 Hz), 6.89(1H, d, J=9.74 Hz), 7.39-7.48(7H, m)

Elemental Analysis for $C_{17}H_{16}N_4OS \cdot 0.15H_2O$

Calcd. C: 62.42; H: 5.02; N: 17.13

Found C: 62.93; H: 5.12; N: 16.82

Example 89

Methyl [3-(2-amino-4-phenyl-1,3-thiazol-5-yl)-6-oxo-1(6H)-pyridazinyl]acetate was obtained in a manner similar to Example 85.

m.p.: 190-193℃ (ethanol - diisopropyl ether)

IR (KBr) : 3427, 3103, 1734, 1672, 1591, 1522 cm^{-1}

ESI/MS : 365$(M+Na)^+$, 343$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 3.69(3H, s), 4.83(2H, s), 6.79(1H, d, J=9.80 Hz), 6.92(1H, d, J=9.80 Hz), 7.40-7.51(7H, m)

Example 90

6-(2-Amino-4-phenyl-1,3-thiazol-5-yl)-2-(2-oxopropyl)-3(2H)-pyridazinone was obtained in a manner similar to Example 85.

m.p.: 216-219℃ (ethanol - diisopropyl ether)

IR (KBr) : 3417, 3093, 1728, 1672, 1593, 1522 cm^{-1}

ESI/MS : 349$(M+Na)^+$, 327$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 2.20(3H, s), 4.94(2H, s), 6.77(1H, d, J=9.80 Hz), 6.91(1H, d, J=9.80 Hz), 7.39-7.47(7H, m)

Elemental Analysis for $C_{16}H_{14}N_4O_2S \cdot 0.2H_2O$

Calcd. C: 58.24; H: 4.40; N: 16.98

Found C: 58.14; H: 4.26; N: 16.79

Example 91

To a solution of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone (300 mg) in dimethylformamide (1.8 mL) was added sodium hydride (60 % in oil) (46.6 mg), and the mixture was stirred for 30 minutes at 50-55℃. Iodoethane (0.259 mL) was added to the mixture, and the resulting mixture was stirred for 10 hours at 50-55℃. The mixture was poured into water (15 mL) to give a solid. The solid was collected by filtration, dried over phosphorous pentoxide and purified by a column chromatography on silica gel with eluting with a mixture of n-hexane and ethyl acetate (80 : 20, v/v) to give 6-[2-(diethylamino)-4-phenyl-1,3-thiazol-5-yl]-2-ethyl-3(2H)-pyridazinone as a syrup (6 mg) and eluting with a mixture of n-hexane and ethyl acetate (60 : 40 v/v) to give 2-ethyl-6-[2-(ethylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone as a solid (11 mg), and eluting wih a mixture of n-hexane and ethyl acetate (20 : 80 v/v) to give 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-ethyl-3(2H)-pyridazinone as a solid (213 mg).

6-[2-(diethylamino)-4-phenyl-1,3-thiazol-5-yl]-2-ethyl-3(2H)-pyridazinone

ESI/MS : 731$(2M+Na)^+$, 377$(M+Na)^+$, 355$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.26(6H, t, J=7.10 Hz), 1.40(3H, t, J=7.20 Hz),

3.55(4H, q, J=7.10 Hz), 4.19(2H, q, J=7.20 Hz), 6.59(1H, d, J=9.72 Hz), 6.84(1H, d, J=9.72 Hz), 7.37-7.41(3H, m), 7.51-7.54(2H, m)

2-ethyl-6-[2-(ethylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone
m.p.: 160-163℃ (diisopropyl ether)
IR (KBr) : 3199, 2968, 166, 1583 cm^{-1}
ESI/MS : 675$(2M+Na)^+$, 349$(M+Na)^+$, 327$(M+H)^+$
^1H NMR ($CDCl_3$, δ) : 1.20(3H, t, J=6.68 Hz), 1.40(3H, t, J=7.20 Hz), 3.21-3.26(2H, m), 4.19(2H, q, J=7.20 Hz), 6.15(1H, br.s), 6.60(1H, d, J=9.72 Hz), 6.84(1H, d, J=9.72 Hz), 7.37-7.41(3H, m), 7.46-7.51(2H, m)

6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-ethyl-3(2H)-pyridazinone
m.p.: 232-235℃ (ethanol - diisopropyl ether)
IR (KBr) : 3357, 3124, 1657, 1583, 1522 cm^{-1}
ESI/MS : 619$(2M+Na)^+$, 321$(M+Na)^+$, 299$(M+H)^+$
^1H NMR (DMSO-d_6, δ) : 1.25(3H, t, J=7.16 Hz), 4.00-4.07(2H, m), 6.71(1H, d, J=9.72 Hz), 6.87(1H, d, J=9.72 Hz), 7.38-7.47(7H, m)
Elemental Analysis for $C_{15}H_{14}N_4OS \cdot 0.2H_2O$
Calcd. C: 59.66; H: 4.81; N: 18.55
Found C: 59.77; H: 4.61; N: 18.47

Example 92

6-(2-Amino-4-phenyl-1,3-thiazol-5-yl)-2-benzyl-3(2H)-pyridazinone and 2-benzyl-6-[2-(benzylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone were obtained in a manner simialar to Example 91.

6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-benzyl-3(2H)-pyridazinone
m.p.: 225-228℃ (ethanol - diisopropyl ether)
IR (KBr) : 1653, 1585 cm^{-1}
ESI/MS : 743$(2M+Na)^+$, 383$(M+Na)^+$, 361$(M+H)^+$
^1H NMR (DMSO-d_6, δ) : 5.20(2H, s), 6.77(1H, d, J=9.76 Hz), 6.89(1H, d, J=9.76 Hz), 7.29-7.51(12H, m)
Elemental Analysis for $C_{20}H_{16}N_4OS \cdot 0.5H_2O$

Calcd. C: 65.02; H: 4.64; N: 15.17
Found C: 65.37; H: 4.39; N: 14.75

2-benzyl-6-[2-(benzylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone
m.p.: 163.5-165℃ (ethanol - diisopropyl ether)
IR (KBr) : 3188, 1657, 1576 cm^{-1}
ESI/MS : 923$(2M+Na)^+$, 473$(M+Na)^+$, 451$(M+H)^+$
^1H NMR (DMSO-d_6, δ) : 4.47(2H, d, J=5.20 Hz), 5.27(2H, s), 6.10(1H, br.s), 6.60(1H, d, J=9.76 Hz), 6.84(1H, d, J=9.76 Hz), 7.30-7.48(15H, m)
Elemental Analysis for $C_{27}H_{22}N_4OS \cdot 0.4H_2O$
Calcd. C: 70.84; H: 5.02; N: 12.24
Found C: 70.86; H: 4.76; N: 12.26

Example 93

2-Allyl-6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone, 2-allyl-6-[2-(allylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone and 2-allyl-6-[2-(diallylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone were obtained in a manner similar to Example 91.

2-allyl-6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone
m.p.: 212-215℃ (ethanol)
IR (KBr) : 3373, 3097, 1655, 1581, 1520 cm^{-1}
ESI/MS : 643$(2M+Na)^+$, 333$(M+Na)^+$, 311$(M+H)^+$
^1H NMR (DMSO-d_6, δ) : 4.62(2H, d, J=5.60 Hz), 5.12-5.23(2H, m), 5.89-5.99(1H, m), 6.75(1H, d, J=9.78 Hz), 6.89(1H, d, J=9.78 Hz), 7.38-7.48(7H, m)
Elemental Analysis for $C_{16}H_{14}N_4OS \cdot 0.1H_2O$
Calcd. C: 61.56; H: 4.58; N: 17.95
Found C: 61.43; H: 4.38; N: 17.87

2-allyl-6-[2-(allylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone
m.p.: 146-147℃ (ethanol - diisopropyl ether)
IR (KBr) : 3190, 1672, 1574 cm^{-1}

ESI/MS : 732($2M+Na)^+$, 373$(M+Na)^+$, 351$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 3.89-3.92(2H, m), 4.75(2H, d, J=6.00 Hz), 5.22-5.37(4H, m), 5.76(1H, br.s), 5.87-6.07(2H, m), 6.62(1H, d, J=9.72 Hz), 6.87(1H, d, J=9.72 Hz), 7.38-7.41(3H, m), 7.47-7.51(2H, m)

Elemental Analysis for $C_{19}H_{18}N_4OS \cdot 0.2H_2O$

Calcd. C: 64.46; H: 5.24; N: 15.82

Found C: 64.61; H: 5.07; N: 15.87

2-allyl-6-[2-(diallylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone

ESI/MS : 803$(2M+Na)^+$, 413$(M+Na)^+$, 391$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 4.12(4H, d, J=5.76 Hz), 4.73-4.76(2H, m), 5.24-5.32(4H, m), 5.81-6.12(3H, m), 6.62(1H, d, J=9.72 Hz), 6.87(1H, d, J=9.72 Hz), 7.37-7.39(3H, m), 7.50-7.54(2H,m)

Example 94

Formic acid (66 mg) was added to a solution of acetic anhydride (74 mg) in dichloromethane (3 ml) under ice-bath cooling. After 30 minutes, 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the reaction mixture. The mixture was stirred for 30 minutes with ice-bath cooling, and then stirred for 1 hour at ambient temperature. Formic acid (0.16 ml) and acetic anhydride (0.2ml) were added to the mixture. The reaction mixture was stirred overnight at ambient temperature. An aqueous sodium hydrogencarbonate solution was added to the reaction mixture, the resulting mixture was extracted with ethyl acetate. The separated organic layer was dried over sodium sulfate. The solvent was removed in vacuo to give a yellow powder, which was collected by filtration to afford 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-ylformamide as yellow powder (80 mg).

mp 232-234℃ (ethanol)

IR (KBr) : 3451, 3033, 1695, 1662, 1585 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 5.13(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.02(1H, d, J=9.6 Hz), 7.3-7.55(5H, m), 8.59(1H, s), 12.2-13.0 (1H, br)

ESI/MS : 341(M+H)$^+$, 363 (M+Na)$^+$

Elemental Analysis for $C_{17}H_{16}N_4O_2S$

Calcd. C: 59.98, H: 4.74, N: 16.46

Found C: 60.06, H: 4.78, N: 16.48

Example 95

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (232 mg), di-t-butyloxycarbonate (170 mg) and triethylamine (90 mg) in dichloromethane (5 ml) was stirred at ambient temperature. 4-Dimethylaminopyridine (50 mg) was added to the reaction mixture under same conditions. After 12 hours, water and ethyl acetate were added to the mixture. The separated organic layer was dried over diatomaceous earth. The solvent was removed in vacuo to give a yellow powder, which was objected to a column chlomatography on silica gel eluting with a mixture of n-hexane and ethyl acetate. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford tert-butyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-ylcarbamate (91 mg).

mp 198-199℃ (ethanol)

IR (KBr) : 3154, 1710, 1648, 1581 cm^{-1}

^{1}H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.7 Hz), 1.52(9H, s), 5.31(1H, 7-plet, J=6.7 Hz), 6.66(1H, d, J=9.6 Hz), 6.92(1H, d, J=9.6 Hz), 7.3-7.55(5H, m), 8.51(1H, br)

ESI/MS : 435 (M+Na)$^+$

Elemental Analysis for $C_{21}H_{24}N_4O_3S$

Calcd. C: 61.15, H: 5.86, N: 13.58

Found C: 60.83, H: 6.21, N: 13.29

Example 96

A mixture of 4-(chloromethyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide (100 mg) and 2-methoxyethylamine (50 mg) in dioxane (1 ml) was stirred

overnight at 80℃. Ethyl acetate and an aqueous sodium hydrogencarbonate solution were added to the reaction mixture at ambient temperature. The separated organic layer was dried over sodium sulfate. The solvent was removed in vacuo to give a yellow powder, which was objected to a column chlomatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-{[(2-methoxyethyl)amino]methyl}benzamide as white powder (10mg).

mp 192-194℃ (diisopropyl ether)

IR (KBr) : 3421, 1648, 1577 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.3-3.8(7H, m), 4.07(2H, s), 5.12(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7 Hz), 7.3-7.7(7H, m), 8.0-8.2(2H, m)

APCI/MS : 504$(M+H)^+$, 526 $(M+Na)^+$

Example 97

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-[(4-methyl-1-piperazinyl)methyl]benzamide was obtained in a manner similar to Example 96.

mp 224-227℃ (diisopropyl ether)

IR (KBr) : 3444, 1648 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.16(3H, s), 2.2-2.5(8H, m), 3.54(2H,s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.6 Hz), 7.03(1H, d, J=9.6Hz), 7.3-7.6(7H, m), 8.0-8.15(2H, m), 12.6-13.2(1H, brs)

ESI/MS : 529 $(M+H)^+$, 551 $(M+Na)^+$

Elemental Analysis for $C_{29}H_{32}N_6O_2S$

Calcd. C: 64.78, H: 6.18, N: 15.63

Found C: 64.76, H: 6.17, N: 15.53

Example 98

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-(1-pyrrolidinylmethyl)benzamide was obtained in a manner similar to Example 96.

mp 221-222℃ (diisopropyl ether)

IR (KBr) : 3421, 1650 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 1.7-1.9(4H, m), 2.6-2.8(4H, m), 3.91(2H,s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.6 Hz), 7.04(1H, d, J=9.6Hz), 7.3-7.7(7H, m), 8.0-8.15(2H, m), 10-13(1H, br)

ESI/MS : 500$(M+H)^+$, 522 $(M+Na)^+$

Elemental Analysis for $C_{28}H_{29}N_5O_2S \cdot 2.6H_2O$

Calcd. C: 61.54, H: 6.31, N: 12.82

Found C: 61.47, H: 6.06, N: 13.00

Example 99

A mixture of 2-isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone hydrobromide (111 mg), 3-tolylisocyanate (40 mg) and triethylamine (33 mg) in dioxane (3 ml) was stirred for 3 hours at ambient temperature. Water and ethyl acetate were added to the reaction mixture at ambient temperature. The separated organic layer was dried over diatomaceous earth. The solvent was removed in vacuo to give a yellow powder, which was objected to a column chlomatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-N-methyl-N'-(3-methylphenyl)urea as yellow white powder (11 mg).

mp 157-158℃ (diisopropyl ether)

IR (KBr) :3565, 1683, 1656 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6Hz), 2.32(3H, s) 3.73(3H, s), 5.14(1H, 7-plet, J=6.6Hz), 6.80(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7 Hz), 7.0-7.6(9H, m), 9.37(1H, brs)

ESI/MS : 460(M+H)$^+$, 482 (M+Na)$^+$

Elemental Analysis for $C_{25}H_{25}N_5O_2S \cdot 0.1\ H_2O$

Calcd. C: 65.08, H: 5.51, N: 15.18

Found C: 65.28, H: 5.56, N: 14.80

Example 100

A mixture of N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-chloroacetamide (200 mg) and 4-aminomethylpyridine (278 mg) in dioxane (4 ml) was stirred overnight at 50℃. Water and ethyl acetate were added to the reaction mixture at ambient temperature. The separated organic layer was dried over diatomaceous earth. The solvent was removed in vacuo to give a yellow powder, which was objected to a column chlomatography on silica gel eluting with a mixture of chloroform and methanol. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to give N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl- 1,3-thiazol-2-yl]-2-[(4-pyridinylmethyl)amino]acetamide as a yellow white powder (105 mg).

mp : 187-188℃(diisopropyl ether)

IR (KBr) : 3336, 1658, 1581 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 3.51(2H, s), 3.81(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), 7.3-7.6(8H, m), 8.05(2H, dd, J=1.5Hz and 4.5Hz)

ESI/MS : 461(M+H)$^+$, 483(M+Na)$^+$

Example 101

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-[(2-pyridinylmethyl)amino]acetamide dihydrochloride was obtained in a manner similar to Example 100.

mp : 252-254℃(diisopropyl ether)

IR (KBr) : 1648 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 4.23(2H, brs), 4.49(2H, brs), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d,

J=9.7Hz), 7.3-7.6(7H, m), 7.85-8.0(1H, m), 8.67 (1H, dd, J=0.8Hz and 4.2Hz), 9.6-10.2(1H, br), 12.6-13.4(1H, br)

ESI/MS : 461(M-2HCl+H)$^+$, 483 (M-2HCl+Na)$^+$

Elemental Analysis for $C_{28}H_{29}N_5O_3S \cdot 0.3H_2O$

Calcd. C: 64.55, H: 5.73, N: 13.44

Found C: 64.72, H: 5.90, N: 12.97

Example 102

2-(1H-Imidazol-1-yl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp : 160-161℃(ethanol)

IR (KBr) : 3451, 1698, 1656 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.25(6H, d, J=6.6 Hz), 5.08(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.80(1H, d, J=9.7 Hz), 6.92(1H, s), 7.02(1H, d, J=9.7Hz), 7.19(1H, s), 7.3-7.6(5H, m), 7.66 (1H, s), 12.81(1H, br)

ESI/MS : 421(M+H)$^+$, 443 (M+Na)$^+$

Elemental Analysis for $C_{21}H_{20}N_6O_2S \cdot 0.8H_2O$

Calcd. C: 58.00, H: 5.01, N: 19.32

Found C: 58.05, H: 5.05, N: 19.26

Example 103

2-(Benzylamino)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp : 144-145℃(ethanol)

IR (KBr) : 3286, 1677, 1658 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 3.48(2H, s), 3.76(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), 7.1-7.6(12H, m)

ESI/MS : 460(M+H)$^+$, 482 (M+Na)$^+$

Elemental Analysis for $C_{25}H_{25}N_5O_2S$

Calcd. C: 65.34, H: 5.48, N: 15.24

Found C: 65.24, H: 5.50 N: 15.24

Example 104

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-[(2-methoxyethyl)amino]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 252-253℃ (ethyl acetate)

IR (KBr) : 3444, 1668, 1658 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 3.2-3.3(2H, br), 3.4-3.7(5H, m), 4.13(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 9.44(2H, br), 13.01(1H, brs)

ESI/MS : 428$(M-HCl+H)^+$, 450 $(M-HCl+Na)^+$

Elemental Analysis for $C_{21}H_{26}ClN_5O_3S \cdot 1.0H_2O$

Calcd. C: 52.33, H: 5.86, N: 14.53

Found C: 52.39, H: 5.77, N: 14.60

Example 105

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(4-methyl-1-piperazinyl)acetamide dihydrochloride was obtained in a manner similar to Example 100.

mp : 244-246℃ (diisopropyl ether)

IR (KBr) : 3428, 1648, cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 2.82(3H, s), 3.3-3.7(8H, m), 4.20(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.67 Hz), 7.02(1H, d, J=9.6Hz), 6.8-7.3(2H, m), 7.3-7.6(5H, m), 13.01(1H, brs)

ESI/MS : 453$(M-2HCl+H)^+$, 475 $(M-2HCl+Na)^+$

Example 106

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(4-morpholinyl)acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 252-253℃ (ethyl acetate)

IR (KBr) : 3426, 1670, 1658 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 3.2-3.5(4H, br),

3.8-4.0(4H, m), 4.2-4.4(2H, brs), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.4-7.55(5H, m), 11.15(1H, brs), 13.13(1H, brs)

ESI/MS : 440(M-HCl+H)$^+$, 462 (M-HCl+Na)$^+$

Elemental Analysis for $C_{22}H_{26}ClN_5O_3S \cdot 0.9H_2O$

Calcd. C: 53.69, H: 5.69, N: 14.23

Found C: 53.69, H: 5.67, N: 14.13

Example 107

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(1-pyrrolidinyl)acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : >250℃ (ethyl acetate)

IR (KBr) : 3423, 1668, 1656 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 1.8-2.1(4H, m), 3.0-3.3(2H, m), 3.4-3.8(2H, m), 4.42 (2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.35-7.6(5H, m), 10.92(1H, brs), 13.09(1H, brs)

ESI/MS : 424(M-HCl+H)$^+$, 446(M-HCl+Na)$^+$

Elemental Analysis for $C_{22}H_{26}ClN_5O_2S \cdot 0.8H_2O$

Calcd. C: 55.70, H: 5.86, N: 14.76

Found C: 55.79, H: 5.78, N: 14.76

Example 108

2-(Dimethylamino)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 232-234℃(ethyl acetate)

IR (KBr) : 3421, 1662 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 2.92(6H, s), 4.33(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 10.57(1H, brs), 13.13(1H, brs)

ESI/MS : 398(M-HCl+H)$^+$, 420(M-HCl+Na)$^+$

Elemental Analysis for $C_{20}H_{24}ClN_5O_2S \cdot 2.2H_2O$

Calcd. C: 50.72, H: 6.04, N: 14.79

Found C: 50.61, H: 5.96, N: 14.70

Example 109

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-{[3-(2-oxo-1-pyrrolidinyl)propyl]amino}acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 207-209℃ (diisopropyl ether)

IR (KBr) : 3424, 1698, 1646 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 1.8-2.0(4H, m), 2.2-2.3(2H, m), 2.9-3.05(2H, br), 3.2-3.3(2H, m), 3.3-3.4(2H, m), 4.05-4.2(2H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 9.37(2H, br)

ESI/MS : 495$(M-HCl+H)^+$, 517$(M-HCl+Na)^+$

Example 110

2-[(2-Hydroxypropyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 209-211℃(diisopropyl ether)

IR (KBr) : 3421, 1664 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.13(3H, d, J=6.3Hz), 1.27(6H, d, J=6.6 Hz), 2.85-3.0(1H, m), 3.05-3.15(1H, m), 3.95-4.05(1H, m), 4.13(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 5.3-5.5(1H, br), 6.83(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 8.99(1H, brs), 9.37(1H, brs), 13.0(1H, br)

ESI/MS : 428$(M-HCl+H)^+$, 450$(M-HCl+Na)^+$

Elemental Analysis for $C_{21}H_{26}ClN_5O_3S \cdot 1.2H_2O$

Calcd. C: 51.92, H: 5.89, N: 14.42

Found C: 51.92, H: 5.78, N: 14.28

Example 111

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-{methyl[2-(2-pyridinyl)ethyl]amino}acetamide was

obtained in a manner similar to Example 100.

mp : 94-96℃ (diisopropyl ether)

IR (KBr) : 1666 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 2.32(3H, s), 2.8-3.0(4H, m), 3.43(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.15-7.25(1H, m), 7.25-7.35(1H, m), 7.4-7.6(5H, m), 7.71(1H, t, J=7.6Hz), 8.67(1H, d, J=7.6Hz), 12.3-12.6(1H, br)

ESI/MS : 489$(M+H)^+$, 511$(M+Na)^+$

Example 112

2-[(2-Hydroxy-2-phenylethyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp: 218-220℃(diisopropyl ether)

IR (KBr) : 3421, 1666, 1650 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.28(6H, d, J=6.6 Hz), 3.1-3.4(2H, m), 4.18(2H, s), 5.02(1H, dd, J=2.7Hz and 10.2Hz), 5.14(1H, 7-plet, J=6.6 Hz), 6.1-6.3(1H, br), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.2-7.6(10H, m), 9.0-9.2(1H, br), 9.4-9.7 (1H, br), 13.0(1H, s)

ESI/MS : 490$(M-HCl+H)^+$, 512$(M-HCl+Na)^+$

Elemental Analysis for $C_{26}H_{28}ClN_5O_3S \cdot 1.0H_2O$

Calcd. C: 57.40, H: 5.56, N: 12.87

Found C: 57.41, H: 5.36, N: 12.77

Example 113

2-[(3-Hydroxypropyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp: 136-142℃ (ethyl acetate)

IR (KBr) : 3421, 1648 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 1.75-1.9(2H, m), 3.0-3.15(2H, m), 3.4-3.6(2H, m), 4.05-4.2(2H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.35-7.6(5H, m), 9.33(2H, br), 12.8-13.2(1H, br)

ESI/MS : 428(M-HCl+H)$^+$, 550(M-HCl+Na)$^+$

Example 114

2-({2-[4-(Aminosulfonyl)phenyl]ethyl}amino)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp: 104-106℃ (diisopropyl ether)

IR (KBr) : 3253, 3224, 1650 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.75-2.9(4H, m), 3.51(2H, s), 5.13(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7Hz), 7.2-7.35(3H, br), 7.35-7.55(7H, m), 7.74(2H, d, J=8.3Hz)

ESI/MS : 553(M+H)$^+$, 575(M+Na)$^+$

Example 115

2-[(2,3-Dihydroxypropyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp: 147-149℃ (diisopropyl ether)

IR (KBr) : 3419, 1650 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.5-2.7(1H, m), 2.85-3.0(1H, m), 3.5-3.9(3H, m), 4.5-4.7(1H, m), 4.9-5.1(1H, m), 5.13(1H, 7-plet, J=6.6 Hz), 6.79(1H, d, J=9.7 Hz), 6.98(1H, d, J=9.7Hz), 7.35-7.6(5H, br)

ESI/MS : 444(M+H)$^+$, 466(M+Na)$^+$

Example 116

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-{[3-(4-morpholinyl)propyl]amino}acetamide dihydrochloride was obtained in a manner similar to Example 100.

mp: 211-213℃ (diisopropyl ether)

IR (KBr) : 3451, 1662 , 1648 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.1-2.25(2H, m), 2.9-3.4(8H, m), 3.7-4.05(4H, m), 4.15(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 9.5-9.7(2H,

br), 11.0-11.4(1H, br), 12.9-13.20(1H, br)

ESI/MS : 497(M-2HCl+H)$^+$, 519(M-2HCl+Na)$^+$

Elemental Analysis for $C_{25}H_{34}Cl_2N_6O_3S \cdot 1.5H_2O$

Calcd. C: 50.33, H: 6.25, N: 14.09

Found C: 50.38, H: 6.24, N: 13.92

Example 117

2-[(2-Hydroxyethyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp: 142-144℃ (diisopropyl ether)

IR (KBr) : 3291, 1693, 1648 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.55-2.70(2H, m), 3.4-3.55(4H, m), 5.13(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), 7.35-7.6(5H, m)

ESI/MS : 414(M+H)$^+$, 436(M+Na)$^+$

Example 118

2-[[2-(Dimethylamino)ethyl](methyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp: 155-157℃ (diisopropyl ether)

IR (KBr) : 1660 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.28(6H, s), 2.40(3H, s), 2.40-2.50(2H, m), 2.55-2.65(2H, m), 3.38(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.35-7.6(5H, m)

ESI/MS : 455(M+H)$^+$, 477(M+Na)$^+$

Elemental Analysis for $C_{23}H_{30}N_6O_2S \cdot 0.1H_2O$

Calcd. C: 60.53, H: 6.67, N: 18.41

Found C: 60.42, H: 6.61, N: 18.27

Example 119

2-{[2-(Dimethylamino)ethyl]amino}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide

dihydrochloride

mp: 136-142℃ (diisopropyl ether)

IR (KBr) : 3421, 1673, 1648 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.85(6H, s), 3.3-3.6(4H, m), 4.21(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 9.81(1H, brs), 10.84(1H, brs), 13.1(1H, br)

ESI/MS : 441$(M-2HCl+H)^+$, 463$(M-2HCl+Na)^+$

Elemental Analysis for $C_{22}H_{30}Cl_2N_6O_2S \cdot 4.0H_2O$

Calcd. C: 45.13, H: 6.54, N: 14.35

Found C: 45.22, H: 6.27, N: 14.15

Example 120

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-[(3-pyridinylmethyl)amino]acetamide was obtained in a manner similar to Example 100.

mp: 156-158℃ (diisopropyl ether)

IR (KBr) : 1664 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 3.50(2H, s), 3.79(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), 7.3-7.55(8H, m), 7.7-7.8(1H, m), 8.4-8.5(1H, m), 8.5-8.6(1H,m)

ESI/MS : 461$(M+H)^+$, 483$(M+Na)^+$

Example 121

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-(1-pyrrolidinyl)propanamide hydrochloride was obtained in a manner similar to Example 100.

mp: 224-225℃ (ethayl acetate)

IR (KBr) : 3421, 1666 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 1.8-2.1(4H, m), 2.9-3.1(4H, m), 3.4-3.6(4H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 10.7-10.9(1H, br), 12.70(1H, s)

ESI/MS : 438$(M-HCl+H)^+$, 460$(M-HCl+Na)^+$

Example 122

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-[(2-methoxyethyl)amino]propanamide was obtained in a manner similar to Example 100.

mp: 167-168℃ (ethanol)

IR (KBr) : 3303, 1658 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.5-2.65(2H, m), 2.65-2.75(2H, m), 2.8-2.9(2H, m), 3.24(3H, s), 3.3-3.45(2H, m), 5.13(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7Hz), 7.05-7.35(1H, br), 7.3-7.6(5H, m)

ESI/MS : 442$(M+H)^+$, 464$(M+Na)^+$

Example 123

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-(4-morpholinyl)propanamide was obtained in a manner similar to Example 100.

mp: 197-198℃ (ethanol)

IR (KBr) : 3423, 1658 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.3-2.45(4H, m), 2.6-2.7(4H, m), 3.5-3.6(4H, m), 5.13(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 12.4-12.5(1H, br)

ESI/MS : 454$(M+H)^+$, 476$(M+Na)^+$

Example 124

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-[(2-pyridinylmethyl)amino]propanamide was obtained in a manner similar to Example 100.

mp: 200-201℃ (ethanol)

IR (KBr) : 3235, 1652 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.6-2.7(2H, m), 2.8-2.9(2H, m), 3.82(2H, s), 5.13(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7Hz), 7.2-7.3(1H, m), 7.3-7.6(7H, m), 7.65-7.8(1H, m), 8.45-8.55(1H, m)

ESI/MS : 475(M+H)$^+$, 479(M+Na)$^+$

Example 125

2-{[2-(Acetylamino)ethyl]amino}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 102-106℃ (ethyl acetate)

IR (KBr) : 3444, 1668, 1648 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 1.86(3H, s), 3.0-3.2(2H, m), 3.3-3.5(2H, m), 4.13(2H, s), 5.13(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 8.2-8.3(1H, m), 9.39(2H, br), 12.9-13.1(1H, br)

ESI/MS : 455(M-HCl+H)$^+$, 477(M-HCl+Na)$^+$

Example 126

2-{[3-(Dimethylamino)propyl]amino}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide dihydrochloride was obtained in a manner similar to Example 100.

mp : 240-242℃ (ethyl acetate)

IR (KBr) : 3490, 1668, 1652 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 2.0-2.2(2H, m), 2.75(6H, s), 3.0-3.2(4H, m), 4.13(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.4-7.6(5H, m), 9.3-10.0(2H, br), 10.0-10.9(1H, br), 12.7-13.3(1H, br)

ESI/MS : 455(M-2HCl+H)$^+$, 477(M-2HCl+Na)$^+$

Example 127

2-{[2-(Diethylamino)ethyl]amino}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide dihydrochloride was obtained in a manner similar to Example 100.

mp : 157-159℃ (ethyl acetate)

IR (KBr) : 3421, 1648 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.1-1.4(12H, m), 3.1-3.3(4H, m), 3.4-3.6(4H, m), 4.22(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz),

7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.7-10.2(2H, br), 10.8-11.3(1H, br), 12.7-13.3(1H, br)
ESI/MS : 469(M-2HCl+H)$^+$

Example 128
2-[[2-(Diethylamino)ethyl](methyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide dihydrochloride was obtained in a manner similar to Example 100.
mp : 227-229℃ (ethyl acetate)
IR (KBr) : 3444, 1650cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 1.1-1.4(12H, m), 2.94(3H, s), 3.1-3.3(4H, m), 3.4-3.6(4H, m), 4.33(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 10.8-11.3(1H, br), 12.7-13.3(1H, br)
ESI/MS : 483(M-2HCl+H)$^+$

Example 129
N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-{[2-(4-morpholinyl)ethyl]amino}acetamide dihydrochloride was obtained in a manner similar to Example 100.
mp : 250-252℃ (ethyl acetate)
IR (KBr) : 3444, 1648cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6Hz), 3.1-4.0(12H, m), 4.22(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.7-10.3(2H, br), 10.8-11.8(1H, br), 12.7-13.3(1H, br)
ESI/MS : 483(M-2HCl+H)$^+$, 505(M-2HCl+Na)$^+$

Example 130
2-(Isopropylamino)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.
mp : >250℃ (ethyl acetate)
IR (KBr) : 3423, 1666cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.1-1.3(12H, m), 3.3-3.5(1H, m), 4.11(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.2-9.3(2H, br), 12.8-13.3(1H, br)
ESI/MS : 412(M-HCl+H)$^+$, 434(M-HCl+Na)$^+$

Example 131

2-(Cyclopropylamino)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.
mp : 123-125℃ (ethyl acetate)
IR (KBr) : 3423, 1648cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 0.65-0.8(2H, m), 0.9-1.05(2H, m), 1.27(6H, d, J=6.6Hz), 2.75-2.9(1H, m), 4.18(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.72(2H, br), 12.8-13.3(1H, br)
ESI/MS : 410(M-HCl+H)$^+$, 432(M-HCl+Na)$^+$

Example 132

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-(1-piperidinyl)acetamide was obtained in a manner similar to Example 100.
mp : 189-190℃ (ethanol)
IR (KBr) : 3241, 1666cm^{-1}
^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6Hz), 1.3-1.6(6H, m), 2.4-2.6(2H, m), 3.2-3.4(4H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.80(1H, d, J=9.7 Hz), 7.01(1H, d, J=9.7Hz), 7.3-7.6(5H, m),11.0-13.0(1H, br)
ESI/MS : 438(M+H)$^+$, 460(M+Na)$^+$

Example 133

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-[(3-methoxypropyl)amino]acetamide hydrochloride was obtained in a manner similar to Example 100.
mp : >250℃ (ethyl acetate)
IR (KBr) : 3444, 1666 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6Hz), 1.8-2.0(2H, m), 3.0-3.15(2H, m), 3.26(3H, s), 3.35-3.5(2H, m), 3.8-4.1(2H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.37(2H, br), 12.8-13.2(1H, br)

ESI/MS : 442(M-HCl+H)$^+$, 464(M-HCl+Na)$^+$

Example 134

2-[(2-Ethoxyethyl)amino]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp : 252-253℃ (ethyl acetate)

IR (KBr) : 3444, 1666 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.16(3H, t, J=7.0Hz), 1.27(6H, d, J=6.6Hz), 3.2-3.3(2H, m), 3.49(2H, q, J=7.0Hz), 3.6-3.75(2H, m), 4.14(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.35(2H, br), 12.8-13.2(1H, br)

ESI/MS : 442(M-HCl+H)$^+$, 464(M-HCl+Na)$^+$

Example 135

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-2-{[2-(1-piperidinyl)ethyl]amino}acetamide dihydrochloride was obtained in a manner similar to Example 100.

mp : >250℃ (ethyl acetate)

IR (KBr) : 1664, 1648 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6Hz), 1.3-2.0(6H, m), 2.8-3.1(2H, m), 3.3-3.7(6H, m), 4.21(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 9.7-10.0(2H, br), 10.3-10.7(1H, br), 12.8-13.2(1H, br)

ESI/MS : 481(M-2HCl+H)$^+$

Example 136

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-(1-piperidinylmethyl)benzamide was obtained in a manner similar to Example 100.

mp: 136-138℃ (isopropyl ether)

IR (KBr) : 3421, 1648, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 1.2-1.65(6H, br), 2.2-2.4(4H, br), 3.51(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.10(2H, d, J=8.1Hz), 12.89(1H, br)

ESI/MS : 514$(M+H)^+$, 536$(M+Na)^+$

Elemental Analysis for $C_{29}H_{31}N_5O_2S \cdot 0.6H_2O$

Calcd. C: 66.41, H: 6.19, N: 13.35

Found C: 66.65, H: 6.21, N: 12.96

Example 137

4-{[[2-(Dimethylamino)ethyl](methyl)amino]methyl}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: 131-133℃ (isopropyl ether)

IR (KBr) : 3442, 1648, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.16(3H, s), 2.21(6H, s), 2.4-2.6(4H, br), 3.58(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.4-7.6(7H, m), 8.11(2H, d, J=8.1Hz)

ESI/MS : 531$(M+H)^+$, 553$(M+Na)^+$

Elemental Analysis for $C_{29}H_{34}N_6O_2S \cdot 0.9H_2O$

Calcd. C: 63.69, H: 6.60, N: 15.37

Found C: 63.79, H: 6.45, N: 15.20

Example 138

4-{[(2-Hydroxyethyl)amino]methyl}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: 111-113℃ (isopropyl ether)

IR (KBr) : 3421, 1650, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.60(2H, t, J=5.8Hz), 3.4-3.6(3H, m), 3.82(2H, s), 4.52(1H, br), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.11(2H, d,

J=8.1Hz)

ESI/MS : 490(M+H)$^+$, 512(M+Na)$^+$

Elemental Analysis for $C_{26}H_{27}N_5O_3S \cdot 1.5H_2O$

Calcd. C: 60.45, H: 5.85, N: 13.56

Found C: 60.43, H: 5.47, N: 13.26

Example 139

4-(1H-Imidazol-1-ylmethyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: >250℃ (isopropyl ether)

IR (KBr) : 3442, 1654, 1581 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.29(6H, d, J=6.6 Hz), 5.15(1H, 7-plet, J=6.6 Hz), 5.32(2H, s), 6.82(1H, d, J=9.7 Hz), 6.94(1H, s), 7.03(1H, d, J=9.7Hz), 7.23(1H, s), 7.3-7.6(7H, m), 7.80(1H, s), 8.12(2H, d, J=8.3Hz)

ESI/MS : 497(M+H)$^+$, 519(M+Na)$^+$

Example 140

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-{[[2-(4-morpholinyl)ethyl]amino}methyl)benzamide was obtained in a manner similar to Example 100.

mp: 86-88℃ (isopropyl ether)

IR (KBr) : 3442, 1652, 1579 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.2-2.7(8H, m), 3.5-3.6(4H, m), 3.82(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 6.9-7.1(1H, br), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.10(2H, d, J=8.1Hz)

ESI/MS : 559(M+H)$^+$, 581(M+Na)$^+$

Example 141

4-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: 115-116℃ (isopropyl ether)

IR (KBr) : 3421, 1650, 1581 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 0.96(6H, t, J=7.1Hz), 1.30(6H, d, J=6.6 Hz), 2.17(3H, s), 2.3-2.7(8H, m), 3.59(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.82(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.11(2H, d, J=8.1Hz)

ESI/MS : 559$(M+H)^+$, 581$(M+Na)^+$

Elemental Analysis for $C_{31}H_{38}N_6O_2S \cdot 0.7H_2O$

Calcd. C: 65.17, H: 6.95, N: 14.71

Found C: 65.22, H: 6.74, N: 14.56

Example 142

4-({[2-(Diethylamino)ethyl]amino}methyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: 158-160℃ (isopropyl ether)

IR (KBr) : 3426, 1660, 1585 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 0.95(6H, t, J=7.1Hz), 1.30(6H, d, J=6.6 Hz), 2.4-2.6(8H, m), 3.81(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.11(2H, d, J=8.1Hz)

ESI/MS : 545$(M+H)^+$, 567$(M+Na)^+$

Elemental Analysis for $C_{30}H_{36}N_6O_2S \cdot 0.1H_2O$

Calcd. C: 65.93, H: 6.68, N: 15.38

Found C: 65.95, H: 6.78, N: 14.94

Example 143

4-({[3-(Dimethylamino)propyl]amino}methyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: 108-110℃ (isopropyl ether)

IR (KBr) : 3424, 1652, 1581 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.29(6H, d, J=6.6 Hz), 1.45-1.7(2H, m), 2.11(6H, s), 2.1-2.4(4H, m), 3.77(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.79(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.10(2H, d, J=8.2Hz)

ESI/MS : 531(M+H)$^+$, 553(M+Na)$^+$

Elemental Analysis for $C_{29}H_{34}N_6O_2S \cdot 1.0H_2O$

Calcd. C: 63.48, H: 6.61, N: 15.32

Found C: 63.62, H: 6.85, N: 15.16

Example 144

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-({[2-(1-piperidinyl)ethyl]amino}methyl)benzamide was obtained in a manner similar to Example 100.

mp: 134-136℃ (isopropyl ether)

IR (KBr) : 3421, 1648, 1579 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 1.2-1.6(6H, m), 2.2-2.7(8H, m), 3.80(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.10(2H, d, J=8.1Hz)

ESI/MS : 557(M+H)$^+$, 579(M+Na)$^+$

Elemental Analysis for $C_{31}H_{36}N_6O_2S \cdot 0.2H_2O$

Calcd. C: 66.45, H: 6.55, N: 15.00

Found C: 66.42, H: 6.53, N: 14.72

Example 145

4-{[(2-Ethoxyethyl)amino]methyl}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.

mp: 153-154℃ (isopropyl ether)

IR (KBr) : 3423, 1656, 1583 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.11(3H, t, J=7.0Hz), 1.30(6H, d, J=6.6 Hz), 2.6-2.7(2H, m), 3.2-3.5(4H, m), 3.81(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.03(1H, d, J=9.6Hz), 7.3-7.6(7H, m), 8.10(2H, d, J=8.2Hz)

ESI/MS : 518(M+H)$^+$, 540(M+Na)$^+$

Elemental Analysis for $C_{28}H_{31}N_5O_3S \cdot 0.2H_2O$

Calcd. C: 64.52, H: 6.07, N: 13.44

Found C: 64.48, H: 6.99, N: 13.33

Example 146

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-{[(3-methoxypropyl)amino]methyl}benzamide was obtained in a manner similar to Example 100.

mp: 169-171℃ (isopropyl ether)

IR (KBr) : 1654, 1583 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 1.67(2H, 5-plet, J=6.7Hz), 2.4-2.65(2H, m), 3.21(3H, s), 3.25-3.45(2H, m), 3.79(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.6Hz), 7.3-7.6(7H, m), 8.10(2H, d, J=8.2Hz)

ESI/MS : 518$(M+H)^+$, 540$(M+Na)^+$

Elemental Analysis for $C_{28}H_{31}N_5O_3S \cdot 0.4H_2O$

Calcd. C: 64.08, H: 6.11, N: 13.34

Found C: 64.07, H: 5.94, N: 13.24

Example 147

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-4-({methyl[2-(2-pyridinyl)ethyl]amino}methyl)benzamide was obtained in a manner similar to Example 100.

mp: 172-174℃ (isopropyl ether)

IR (KBr) : 3307, 1648, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.30(6H, d, J=6.6 Hz), 2.22(3H, s), 2.6-2.8(2H, m), 2.8-3.0(2H, m), 3.61(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.6Hz), 7.1-7.8(10H, m), 8.07(2H, d, J=8.2Hz), 8.4-8.45(1H, m), 12.88(1H, br)

ESI/MS : 565$(M+H)^+$, 587$(M+Na)^+$

Elemental Analysis for $C_{32}H_{32}N_6O_2S$

Calcd. C: 68.06, H: 5.71, N: 14.88

Found C: 68.09, H: 5.76, N: 14.66

Example 148

2-{[(2R)-2-Hydroxypropyl]amino}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp: 206-208℃ (ethyl acetate-diisopropyl ether)

IR (KBr) : 3411, 1646, 1579 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.16(3H, d, J=5.2Hz), 1.28(6H, d, J=6.6 Hz), 2.7-3.2(2H, s), 3.8-4.2(3H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 8.7-9.5(2H, br), 12.99(1H, br)

ESI/MS : 428(M-HCl+H)$^+$, 450(M-HCl+Na)$^+$

Example 149

2-{[(2S)-2-Hydroxypropyl]amino}-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide hydrochloride was obtained in a manner similar to Example 100.

mp: 211-213℃ (ethyl acetate-diisopropyl ether)

IR (KBr) : 3438, 1644, 1583 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.16(3H, d, J=5.2Hz), 1.28(6H, d, J=6.6 Hz), 2.7-3.2(2H, s), 3.8-4.2(3H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.83(1H, d, J=9.7 Hz), 7.04(1H, d, J=9.7Hz), 7.3-7.6(5H, m), 8.7-9.5(2H, br), 12.99(1H, br)

ESI/MS : 428(M-HCl+H)$^+$, 450(M-HCl+Na)$^+$

Example 150

2-(4-Acetyl-1-piperazinyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]acetamide was obtained in a manner similar to Example 100.

mp 220-222 ℃ (diisopropyl ether)

IR (KBr) : 3451, 1698, 1656 cm^{-1}

^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 1.99(3H, s), 2.4-2.65(4H, m), 3.2-3.6(6H, m), 5.14(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.02(1H, d, J=9.7Hz), , 7.3-7.6(5H, m), 12.2-12.6 (1H, brs)

ESI/MS : 481(M+H)$^+$, 503 (M+Na)$^+$

Example 151

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-(4-fluorophenyl)-1,3-thiazol-2-yl]-2-(4-morpholinyl)acetamide

hydrochloride was obtained in a manner similar to Example 100.
mp >250 ℃ (diisopropyl ether)
IR (KBr) : 3451, 1698, 1656 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.27(6H, d, J=6.6 Hz), 3.2-4.0(8H, m), 4.36(2H, s), 5.14(1H, 7-plet, J=6.6 Hz), 6.85(1H, d, J=9.7 Hz), 7.07(1H, d, J=9.7Hz), 7.2-7.4(2H, m), 7.5-7.65(2H, m), 10.8-11.4 (1H, brs), 13.0-13.5(1H, br)
ESI/MS : 458$(M-HCl+H)^+$, 480 $(M-HCl+Na)^+$

Example 152

4-[(Isopropylamino)methyl]-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]benzamide was obtained in a manner similar to Example 100.
mp: 139-141℃ (isopropyl ether)
IR (KBr) : 3426, 1654, 1581 cm^{-1}
^1H NMR (DMSO-d_6, δ) : 1.04(6H, d, J =6.2Hz), 1.30(6H, d, J=6.6 Hz), 2.76(1H, m), 3.81(2H, s), 5.15(1H, 7-plet, J=6.6 Hz), 6.81(1H, d, J=9.7 Hz), 7.03(1H, d, J=9.7Hz), 7.3-7.6(7H, m), 8.11(2H, d, J=8.1Hz)
ESI/MS : 488$(M+H)^+$, 510$(M+Na)^+$
Elemental Analysis for $C_{27}H_{29}N_5O_2S \cdot 0.4H_2O$
Calcd. C: 65.54, H: 6.07, N: 14.15
Found C: 65.54, H: 5.97, N: 14.06

Example 153

A mixture of 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl-3(2H)-pyridazinone (2.0 g) and triethylamine (80.94 ml) in dichloromethane (40 ml) was stirred at 0℃. 3-Chloropropionyl chloride (0.64 ml) was added to the solution with stirring. Chloroform and 1N-hydrochloric acid were added to the reaction mixture at ambient temperature. The separated organic layer was dried over sodium sulfate. The solvent was removed in vacuo to give a yellow powder, which was objected to a column chlomatography on silica gel eluting with ethyl acetate. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring.

The powder was collected by filtration to afford N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazol-2-yl]-3-chloropropanamide (0.64g) as a white powder.

^{1}H NMR ($CDCl_3$ δ) : 1.3-1.45(6H, m), 1.7-1.8(1H, m), 2.1-2.2(1H, m), 3.5-3.6(1H, m), 5.3-5.6(2H, m), 6.7-6.8(1H, m), 6.9-7.0(1H, m), 7.35-7.6(5H, m), 10.7(1H, br)

ESI/MS nega: 401(M-H)$^-$

Example 154

A mixture of 6-(1-bromo-2-oxo-2-phenylethyl)-2-isopropyl-3(2H)-pyridazinone (150 mg) and 1-hexyl-2-thiourea (108 mg) in dioxane (1 ml) was stirred overnight at 80℃. The solvent was removed in vacuo to give yellow powder, which was objected to a column chlomatography on silicagel eluting with a mixture of chloroform and methanol (20:1). The solvent was removed in vacuo to afford a yellow powder, which was suspended in a mixture of ethyl acetate and methanol with stirring. The powder was collected by filtration to afford 6-(2-amino-4-phenyl-1,3-thiazol-5-yl)-2-isopropyl- 3(2H)-pyridazinone hydrobromide as a yellow powder (6.51 g).

IR (KBr) :3421, 1629, 1577 cm^{-1}

^{1}H NMR (DMSO-d_6, δ) : 1.26(6H, d, J=6.6 Hz), 4.0-5.0(2H, br), 5.10(1H, 7-plet, J=6.6 Hz), 6.80(2H, s), 7.5-7.6(5H, m)

mp >250 ℃ (diisopropyl ether)

ESI/MS : 313$(M+H)^+$, 335 $(M+Na)^+$

Example 155

A mixture of 2-isopropyl-6-(2-{[3-(1-piperidyl)ethyl]amino}-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone(50 mg) and 4N-hydrochloric acid in ethyl acetate (0.3ml) in methanol (2 ml) was stirred at ambient temperature. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford 2-isopropyl-6-(2-{[3-(1-piperidyl)ethyl]amino}-4-phenyl-1,3-thiazol- 5-yl)-3(2H)-pyridazinone dihydrochloride as a yellow powder (30 mg).

mp : >250 ℃ (diisopropyl ether)

^{1}H NMR (DMSO-d_6, δ) : 1.25(6H, d, J=6.6 Hz), 1.2-1.5(2H, m), 1.5-1.9(4H, m), 2.8-3.1(2H, m), 3.2-3.4(2H, m), 3.4-3.6(2H, m), 3.7-3.9(2H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.74(1H, d, J =9.8Hz), 6.87(1H, d, J =9.8Hz), 7.3-7.6(5H, m), 8.75(1H, br), 10.46(1H, br)

Example 156

A mixture of 2-isopropyl-6-(2-{[2-(4-morpholinyl)ethyl]amino}-4-phenyl-1,3- thiazol-5-yl)-3(2H)-pyridazinone (50 mg) and 4N-hydrochloric acid in ethyl acetate (0.3ml) in methanol (2 ml) was stirred at ambient temperature. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford 2-isopropyl-6-(2-{[2-(4-morpholinyl)ethyl]amino}-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone dihydrochloride as yellow powder (30 mg).

mp : 140-143℃ (isopropyl ether)

^{1}H NMR (DMSO-d_6, δ) : 1.25(6H, d, J=6.6 Hz), 3.1-4.3(12H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.74(1H, d, J =9.7Hz), 6.88(1H, d, J =9.7Hz), 7.3-7.6(5H, m), 8.65(1H, br), 11.16 (1H, br)

Example 157

A mixture of 2-isopropyl-6-(2-{[3-(4-morpholinyl)propyl]amino}-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone (50 mg) and 4N-hydrochloric acid in ethyl acetate (0.3ml) in methanol (2 ml) was stirred at ambient temperature. The solvent was removed in vacuo to afford a yellow powder, which was suspended in diisopropyl ether with stirring. The powder was collected by filtration to afford 2-isopropyl-6-(2-{[3-(4-morpholinyl)propyl]amino}-4-phenyl-1,3-thiazol-5-yl)-3(2H)-pyridazinone dihydrochloride as yellow powder (30 mg).

mp : 150-153 ℃ (diisopropyl ether)

^{1}H NMR (DMSO-d_6, δ) : 1.26(6H, d, J=6.6 Hz), 1.9-2.2(2H, m), 2.9-3.6(8H, m), 3.7-4.0(4H, m), 5.10(1H, 7-plet, J=6.6 Hz), 6.74(1H, d, J =9.7Hz), 6.83(1H, d, J =9.7Hz), 7.3-7.6(5H, m), 9.17(1H, br), 11.37 (1H, br)

Example 158

A mixture of ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (164 mg) and potassium tert-butoxide (17 mg) in formamide (1.64 mL) was heated for 6 hours at 100-105℃. Water (2 mL) was added to the reaction mixture to obtain a solid. The solid was collected by filtration, dried over phosphorous petoxide and purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 20 : 80, v/v) to give 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (49 mg).

m.p.: >250℃ (methanol - diisopropyl ether)

IR (KBr) : 3454, 3184, 1699, 1676, 1579 cm^{-1}

ESI/MS : 321$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 6.82(1H, d, J=9.94 Hz), 7.06(1H, d, J=9.94 Hz), 7.45-7.49(3H, m), 7.57-7.63(2H, m), 7.98(1H, br.s), 8.25(1H, br.s), 13.37(1H, br.s)

Elemental Analysis for $C_{14}H_{10}N_4O_2S$

Calcd. C: 56.37; H: 3.38; N: 18.78

Found C: 56.05; H: 3.28; N: 18.59

Example 159

A mixture of ethyl 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (171 mg) and potassium tert-butoxide (17 mg) in formamide (1.71 mL) was heated for 6 hours at 100-105℃. Water (2 mL) was added to the reaction mixture to obtain a solid. The solid was collected by filtration, dried over phosphorous petoxide and recrystallized from ethanol to give 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (126 mg).

m.p.: 231-232℃ (ethanol)

IR (KBr) : 3371, 3147, 1693, 1664, 1587 cm^{-1}

ESI/MS : 335$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 3.70(3H, s), 6.88(1H, d, J=9.74 Hz), 7.07(1H, d, J=9.74 Hz), 7.45-7.50(3H, m), 7.58-7.64(2H, m), 7.98(1H, br.s), 8.26(1H,

br.s)

Elemental Analysis for $C_{15}H_{12}N_4O_2S$

Calcd. C: 57.68; H: 3.87; N: 17.94

Found C: 57.57; H: 3.79; N: 17.90

Example 160

5-(1-Ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 159.

m.p.: 231-232.5℃ (ethanol)

IR (KBr) : 3363, 3153, 1693, 1660, 1585 cm^{-1}

ESI/MS : 349$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 1.27(3H, t, J=7.17 Hz), 4.10(2H, q, J=7.17 Hz), 6.89(1H, d, J=9.78 Hz), 7.12(1H, d, J=9.78 Hz), 7.45-7.50(3H, m), 7.56-7.63(2H, m), 7.98(1H, br.s), 8.26(1H, br.s)

Elemental Analysis for $C_{16}H_{14}N_4O_2S$

Calcd. C: 58.88; H: 4.32; N: 17.17

Found C: 58.99; H: 4.22; N: 17.17

Example 161

5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamidewas obtained in a manner similar to Example 159.

m.p.: 222-223℃ (ethanol)

IR (KBr) : 3464, 3132, 1685, 1664, 1585 cm^{-1}

ESI/MS : 363$(M+Na)^+$, 341$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.61 Hz), 5.13(1H, 7-plet, J=6.61 Hz), 6.88(1H, d, J=9.70 Hz), 7.15(1H, d, J=9.70 Hz), 7.43-7.50(3H, m), 7.55-7.62(2H, m), 7.97(1H, br.s), 8.25(1H, br.s)

Elemental Analysis for $C_{17}H_{16}N_4O_2S$

Calcd. C: 59.98; H: 4.74; N: 16.46

Found C: 60.13; H: 4.74; N: 16.45

Example 162

5-(1-Allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-

2-carboxamide was obtained in a manner similar to Example 159.

m.p.: 198-199.5℃ (ethanol)

IR (KBr) : 1691, 1664 cm^{-1}

ESI/MS : 361$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 4.78-4.82(2H, m), 5.27-5.38(2H, m), 5.76(1H, br.s), 5.93-6.11(1H, m), 6.75(1H, d, J=9.70 Hz), 6.96(1H, d, J=9.70 Hz), 7.19(1H, br.s), 7.43-7.57(5H, m)

Elemental Analysis for $C_{17}H_{14}N_4O_2S$

Calcd. C: 60.34; H: 4.17; N: 16.56

Found C: 60.45; H: 4.18; N: 16.63

Example 163

4-(2-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 159.

m.p.: 213-215℃ (ethanol)

IR (KBr) : 3465, 3143, 1689, 1664, 1585 cm^{-1}

ESI/MS : 381$(M+Na)^+$, 359$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.61 Hz), 5.28(1H, 7-plet, J=6.61 Hz), 5.69(1H, br.s), 6.77(1H, d, J=9.62 Hz), 7.00(1H, d, J=9.62 Hz), 7.10-7.60(5H, m)

Elemental Analysis for $C_{17}H_{15}FN_4O_2S$

Calcd. C: 56.97; H: 4.22; N: 15.63

Found C: 57.18; H: 4.28; N: 15.61

Example 164

4-(3-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 159.

m.p.: 248-250℃ (ethanol)

IR (KBr) : 3473, 3134, 1687, 1653, 1585 cm^{-1}

ESI/MS : 739$(2M+Na)^+$, 381$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.62 Hz), 5.32(1H, 7-plet, J=6.62 Hz), 5.72(1H, br.s), 6.77(1H, d, J=9.61 Hz), 7.01(1H, d, J=9.61 Hz),

7.10-7.20(2H, m), 7.26-7.50(3H, m)
Elemental Analysis for $C_{17}H_{15}FN_4O_2S$
Calcd. C: 56.97; H: 4.22; N: 15.63
Found C: 57.13; H: 4.27; N: 15.55

Example 165

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 159.
m.p.: 226.5-227.5℃ (ethanol)
IR (KBr) : 3473, 1691, 1664, 1587 cm^{-1}
ESI/MS : 381$(M+Na)^+$
^1H NMR ($CDCl_3$, δ) : 1.23(6H, d, J=6.60 Hz), 5.12(1H, 7-plet, J=6.60 Hz), 6.90(1H, d, J=9.60 Hz), 7.19(1H, d, J=9.60 Hz), 7.24-7.36(2H, m), 7.59-7.68(2H, m), 7.97(1H, br.s), 8.27(1H, br.s)
Elemental Analysis for $C_{17}H_{15}FN_4O_2S$
Calcd. C: 56.97; H: 4.22; N: 15.63
Found C: 56.87; H: 4.14; N: 15.65

Example 166

4-(3-Chlorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 159.
m.p.: 232-234.5℃ (ethanol)
IR (KBr) : 3365, 3153, 1689, 1653, 1579 cm^{-1}
ESI/MS : 773 and 771$(2M+Na)^+$, 399 and 337$(M+Na)^+$
^1H NMR (DMSO-d_6, δ) : 1.21(6H, d, J=6.58 Hz), 5.12(1H, 7-plet, J=6.58 Hz), 6.93(1H, d, J=9.66 Hz), 7.30(1H, d, J=9.66 Hz), 7.42-7.75(3H, m), 7.74(1H, s), 8.01(1H, br.s), 8.34(1H, br.s)
Elemental Analysis for $C_{17}H_{15}ClN_4O_2S$
Calcd. C: 54.47; H: 4.03; N: 14.95
Found C: 54.71; H: 4.09; N: 14.82

Example 167

A mixture of ethyl 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (185 mg) and potassium tert-butoxide (17 mg) in formamide (1.85 mL) was heated for 6 hours at 100-105℃. Water (2 mL) was added to the reaction mixture to obtain a solid. The solid was collected by filtration, dried over phosphorous petoxide and recrystallized from a mixture of ethanol and diisopropyl ether to give 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (124 mg).

m.p.: 201-202℃ (ethanol - diisopropyl ether)

IR (KBr) : 3163, 1697, 1664, 1585 cm^{-1}

ESI/MS : 363$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 0.89(3H, t, J=7.38 Hz), 1.62-1.81(2H, m), 4.04(2H, t, J=7.09 Hz), 6.90(1H, d, J=9.64 Hz), 7.12(1H, d, J=9.64 Hz), 7.45-7.50(3H, m), 7.57-7.63(2H, m), 7.98(1H, br.s), 8.26(1H, br.s)

Elemental Analysis for $C_{17}H_{16}N_4O_2S$

Calcd. C: 59.98; H: 4.74; N: 16.46

Found C: 60.07; H: 4.65; N: 16.43

Example 168

5-[1-(2-Methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 167.

m.p.: 198-199.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3403, 3161, 1684, 1658, 1589 cm^{-1}

ESI/MS : 379$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 3.26(3H, s), 3.68(2H, t, J=5.55 Hz), 4.26(2H, t, J=5.55 Hz), 6.90(1H, d, J=9.64 Hz), 7.11(1H, d, J=9.64 Hz), 7.45-7.49(3H, m), 7.57-7.63(2H, m), 7.98(1H, br.s), 8.27(1H, br.s)

Elemental Analysis for $C_{17}H_{16}N_4O_3S$

Calcd. C: 57.29; H: 4.52; N: 15.72

Found C: 57.29; H: 4.44; N: 15.69

Example 169

In a sealed tube, a mixture of ethyl 5-(6-oxo-1,6-dihydro-3-

pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (164 mg) and propylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from ethanol to give 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-propyl-1,3-thiazole-2-carboxamide as a solid (133 mg).

m.p.: 232-233℃ (ethanol)

IR (KBr) : 3363, 1680, 1662, 1593, 1527 cm^{-1}

ESI/MS : 363$(M+Na)^+$, 341$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 0.88(3H, t, J=7.40 Hz), 1.51-1.59(2H, m), 3.21-3.28(2H, m), 6.83(1H, d, J=9.92 Hz), 7.05(1H, d, J=9.92 Hz), 7.46-7.50(3H, m), 7.57-7.61(2H, m), 8.93(1H, t, J=6.02 Hz), 13.37(1H, s)

Elemental Analysis for $C_{17}H_{16}N_4O_2S$

Calcd. C: 59.98; H: 4.74; N: 16.46

Found C: 59.96; H: 4.83; N: 16.31

Example 170

In a sealed tube, a mixture of ethyl 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (171 mg) and propylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from diisopropyl ether to give 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-propyl-1,3-thiazole-2-carboxamide as a solid (162 mg).

m.p.: 108-109℃ (diisopropyl ether)

IR (KBr) : 3379, 1678, 1651, 1595, 1525 cm^{-1}

ESI/MS : 377$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.42 Hz), 1.58-1.73(2H, m), 3.38-3.50(2H, m), 3.84(3H, s), 6.72(1H, d, J=9.62 Hz), 6.94(1H, d, J=9.62 Hz), 7.31(1H, br.s), 7.41-7.56(5H, m)

Elemental Analysis for $C_{18}H_{18}N_4O_2S$

Calcd. C: 61.00; H: 5.12; N: 15.81

Found C: 61.01; H: 5.16; N: 15.72

Example 171

In a sealed tube, a mixture of ethyl 5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (178 mg) and propylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-propyl-1,3-thiazole-2-carboxamide as a solid (113 mg).

m.p.: 106.5-107.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3319, 1672, 1653, 1589, 1531 cm^{-1}

ESI/MS : 391$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.42 Hz), 1.42(3H, t, J=7.21 Hz), 1.60-1.74(2H, m), 3.38-3.50(2H, m), 4.25(2H, q, J=7.21 Hz), 6.72(1H, d, J=9.68 Hz), 6.94(1H, d, J=9.68 Hz), 7.31(1H, br.s), 7.43-7.56(5H, m)

Elemental Analysis for $C_{19}H_{20}N_4O_2S$

Calcd. C: 61.94; H: 5.47; N: 15.21

Found C: 61.93; H: 5.50; N: 15.20

Example 172

In a sealed tube, a mixture of ethyl 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (185 mg) and propylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-propyl-1,3-thiazole-2-carboxamide as a solid (123 mg).

m.p.: 121-122℃ (ethanol - diisopropyl ether)

IR (KBr) : 3319, 1676, 1651, 1593, 1539 cm^{-1}

ESI/MS : 405$(M+Na)^+$, 383$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.99(3H, t, J=7.42 Hz), 1.00(3H, t, J=7.40 Hz), 1.64-1.70(2H, m), 1.84-1.90(2H, m), 3.41-3.47(2H, m), 4.16(2H, q,

J=7.36 Hz), 6.72(1H, d, J=9.72 Hz), 6.94(1H, d, J=9.72 Hz), 7.31(1H, br.s), 7.44-7.48(3H, m), 7.51-7.55(2H, m)

Elemental Analysis for $C_{20}H_{22}N_4O_2S$

Calcd. C: 62.81; H: 5.80; N: 14.65

Found C: 62.75; H: 5.81; N: 14.59

Example 173

In a sealed tube, a mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and propylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) and crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-propyl-1,3-thiazole-2-carboxamide as a solid (82 mg).

m.p.: 141-142℃ (ethanol - diisopropyl ether)

IR (KBr) : 3273, 1672, 1651, 1541 cm^{-1}

ESI/MS : 787$(2M+Na)^+$, 405$(M+Na)^+$, 383$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.36 Hz), 1.38(6H, d, J=6.62 Hz), 1.59-1.73(2H, m), 3.39-3.50(2H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.71(1H, d, J=9.60 Hz), 6.95(1H, d, J=9.60 Hz), 7.26-7.35(1H, m), 7.43-7.57(5H, m)

Elemental Analysis for $C_{20}H_{22}N_4O_2S$

Calcd. C: 62.81; H: 5.80; N: 14.65

Found C: 62.85; H: 5.88; N: 14.67

Example 174

In a sealed tube, a mixture of ethyl 5-(1-benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (105 mg) and propylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-benzyl-6-oxo-1,6-dihydro-

3-pyridazinyl)-4-phenyl-N-propyl-1,3-thiazole-2-carboxamide as a solid (64 mg).

m.p.: 120-121℃ (ethanol - diisopropyl ether)

IR (KBr) : 3350, 1674, 1664, 1589, 1537 cm^{-1}

ESI/MS : 883$(2M+Na)^+$, 453$(M+Na)^+$, 431$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.40 Hz), 1.58-1.74(2H, m), 3.38-3.50(2H, m), 5.33(2H, s), 6.71(1H, d, J=9.77 Hz), 6.91(1H, d, J=9.77 Hz), 7.26-7.53(11H, m)

Elemental Analysis for $C_{24}H_{22}N_4O_2S$

Calcd. C: 66.96; H: 5.15; N: 13.01

Found C: 66.84; H: 5.15; N: 12.98

Example 175

In a sealed tube, a mixture of ethyl 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (100 mg) and propylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) and crystallized from diisopropyl ether to give 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-propyl-1,3-thiazole-2-carboxamide as a solid (86 mg).

m.p.: 146.5-147.5℃ (diisopropyl ether)

IR (KBr) : 3275, 1674, 1651, 1541 cm^{-1}

ESI/MS : 423$(M+Na)^+$, 401$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.40 Hz), 1.13(6H, d, J=6.62 Hz), 1.62-1.70(2H, m), 3.41-3.48(2H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.75(1H, d, J=9.68 Hz), 6.95(1H, d, J=9.68 Hz), 7.12-7.18(2H, m), 7.28(1H, t, J=5.72 Hz), 7.51-7.55(2H, m)

Elemental Analysis for $C_{20}H_{21}FN_4O_2S$

Calcd. C: 59.98; H: 5.29; N: 13.99

Found C: 60.24; H: 5.40; N: 13.90

Example 176

In a sealed tube, a mixture of ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (164 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from ethanol to give N-isopropyl-5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (137 mg).

m.p.: >250℃ (ethanol)

IR (KBr) : 3278, 1682, 1651, 1591, 1541 cm^{-1}

ESI/MS : 363$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 1.20(6H, d, J=6.60 Hz), 4.09-415(1H, m), 6.83(1H, d, J=9.92 Hz), 7.04(1H, d, J=9.92 Hz), 7.46-7.50(3H, m), 7.59-7.62(2H, m), 8.68(1H, d, J=8.44 Hz), 13.28(1H, br.s)

Elemental Analysis for $C_{17}H_{16}N_4O_2S$

Calcd. C: 59.98; H: 4.74; N: 16.46

Found C: 60.06; H: 4.75; N: 16.46

Example 177

In a sealed tube, a mixture of ethyl 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (171 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-isopropyl-5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (124 mg).

m.p.: 154-154.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3307, 1680, 1645, 1595, 1535 cm^{-1}

ESI/MS : 377$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.60 Hz), 3.84(3H, s), 4.25-4.30(1H, m), 6.73(1H, d, J=9.72 Hz), 6.94(1H, d, J=9.72 Hz), 7.11(1H, d, J=8.10 Hz), 7.44-7.48(3H, m), 7.51-7.55(2H, m)

Elemental Analysis for $C_{18}H_{18}N_4O_2S$

Calcd. C: 61.00; H: 5.12; N: 15.81

Found C: 61.00; H: 5.15; N: 15.76

Example 178

In a sealed tube, a mixture of ethyl 5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (178 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-isopropyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (104mg).

m.p.: 152.5-153℃ (ethanol - diisopropyl ether)

IR (KBr) : 3300, 1674, 1651, 1593, 1554 cm^{-1}

ESI/MS : 391$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.60 Hz), 1.42(3H, t, J=7.20 Hz), 4.22-4.31(3H, m), 6.72(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.11(1H, d, J=8.32 Hz), 7.44-7.48(3H, m), 7.52-7.55(2H, m)

Elemental Analysis for $C_{19}H_{20}N_4O_2S$

Calcd. C: 61.94; H: 5.47; N: 15.21

Found C: 62.00; H: 5.49; N: 15.21

Example 179

In a sealed tube, a mixture of ethyl 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (185 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-isopropyl-5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (108 mg).

m.p.: 146.5-147.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3313, 1676, 1651, 1593,1531 cm^{-1}

ESI/MS : 787$(2M+Na)^+$, 405$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.42 Hz), 1.29(6H, d, J=6.56 Hz),

1.83-1.91(2H, m), 4.16(2H, t, J=7.34 Hz), 4.24-4.31(1H, m), 6.72(1H, d, J=9.68 Hz), 6.92(1H, d, J=9.68 Hz), 7.11(1H, d, J=8.08 Hz), 7.44-7.48(3H, m), 7.52-7.55(2H, m)

Elemental Analysis for $C_{20}H_{22}N_4O_2S$

Calcd. C: 62.81; H: 5.80; N: 14.65

Found C: 62.89; H: 5.83; N: 14.62

Example 180

In a sealed tube, a mixture of (100 mg) and isopropylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) and crystallized from a mixture of diisopropyl ether and n-hexane to give N-isopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (86 mg).

m.p.: 131-132.5℃ (diisopropyl ether - n-hexane)

IR (KBr) : 3273, 1666, 1643, 1534 cm^{-1}

ESI/MS : 787$(2M+Na)^+$, 405$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.28(6H, d, J=6.56 Hz), 1.38(6H, d, J=6.60 Hz), 4.22-4.34(1H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.70(1H, d, J=9.60 Hz), 6.94(1H, d, J=9.60 Hz), 7.11(1H, d, J=8.04 Hz), 7.43-7.57(5H, m)

Elemental Analysis for $C_{20}H_{22}N_4O_2S$

Calcd. C: 62.81; H: 5.80; N: 14.65

Found C: 63.07; H: 5.98; N: 14.63

Example 181

In a sealed tube, a mixture of ethyl 5-(1-allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (184 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from ethanol to give 5-(1-allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-isopropyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (152 mg).

m.p.: 166-167℃ (ethanol)

IR (KBr) : 3305, 1678, 1647, 1593, 1531 cm^{-1}

ESI/MS : 403$(M+Na)^+$, 381$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.29(6H, d, J=6.56 Hz), 4.24-4.30(1H, m), 4.77-4.81(2H, m), 5.28-5.36(2H, m), 5.97-6.06(1H, m), 6.74(1H, d, J=9.72 Hz), 6.94(1H, d, J=9.72 Hz), 7.11(1H, d, J=8.10 Hz), 7.44-7.48(3H, m), 7.52-7.55(2H, m)

Elemental Analysis for $C_{20}H_{20}N_4O_2S$

Calcd. C: 63.14; H: 5.30; N: 14.73

Found C: 63.09; H: 5.32; N: 14.66

Example 182

In a sealed tube, a mixture of ethyl 5-(1-benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (105 mg) and isopropylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-isopropyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (88 mg).

m.p.: 163.5-165℃ (ethanol - diisopropyl ether)

IR (KBr) : 3288, 1674, 1649, 1593, 1539 cm^{-1}

ESI/MS : 883$(2M+Na)^+$, 453$(M+Na)^+$, 431$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.29(6H, d, J=6.60 Hz), 4.25-4.32(1H, m), 5.33(2H, s), 6.71(1H, d, J=9.72 Hz), 6.91(1H, d, J=9.72 Hz), 7.11(1H, d, J=8.10 Hz), 7.30-7.53(10H, m)

Elemental Analysis for $C_{24}H_{22}N_4O_2S$

Calcd. C: 66.96; H: 5.15; N: 13.01

Found C: 66.73; H: 5.13; N: 12.94

Example 183

In a sealed tube, a mixture of ethyl 5-[1-(2-methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-1,3-thiazole-2-carboxylate (96.4 mg) and isopropylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated

for 70 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-isopropyl-5-[1-(2-methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-1,3-thiazole-2-carboxamide as a solid (83 mg).

m.p.: 172-172.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3294, 1670, 1649, 1591, 1537 cm^{-1}

ESI/MS : 819$(2M+Na)^+$, 421$(M+Na)^+$, 399$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.29(6H, d, J=6.58 Hz), 3.40(3H, s), 3.83(2H, t, J=5.60 Hz), 4.25-4.31(1H, m), 4.40(2H, t, J=5.60 Hz), 6.72(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.11(1H, d, J=8.12 Hz), 7.45-7.48(3H, m), 7.52-7.56(2H, m)

Elemental Analysis for $C_{20}H_{22}N_4O_3S$

Calcd. C: 60.28; H: 5.56; N: 14.06

Found C: 60.29; H: 5.59; N: 14.04

Example 184

In a sealed tube, a mixture of ethyl 4-(2-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (201 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 80 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and n-hexane to give 4-(2-fluorophenyl)-N-isopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (132 mg).

m.p.: 129-130.5℃ (ethanol - n-hexane)

IR (KBr) : 3317, 1678, 1655, 1531 cm^{-1}

ESI/MS : 423$(M+Na)^+$, 401$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.29(12H, d, J=6.62 Hz), 4.18-4.37(1H, m), 5.27(1H, 7-plet, J=6.62 Hz), 6.76(1H, d, J=9.62 Hz), 6.99(1H, d, J=9.62 Hz), 7.03-7.35(3H, m), 7.40-7.65(2H, m)

Elemental Analysis for $C_{20}H_{21}FN_4O_2S$

Calcd. C: 59.98; H: 5.29; N: 13.99

Found C: 60.05; H: 5.32; N: 13.97

Example 185

In a sealed tube, a mixture of ethyl 4-(3-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (201 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 80 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from ethanol to give 4-(3-fluorophenyl)-N-isopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (133 mg).

m.p.: 103.5-105.5℃ (ethanol - n-hexane)

IR (KBr) : 3286, 1662, 1653, 1587, 1537 cm^{-1}

ESI/MS : 823$(2M+Na)^+$, 423$(M+Na)^+$, 401$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.60 Hz), 1.36(6H, d, J=6.60 Hz), 4.20-4.37(1H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.76(1H, d, J=9.84 Hz), 6.99(1H, d, J=9.84 Hz), 7.10-7.50(5H, m)

Elemental Analysis for $C_{20}H_{21}FN_4O_2S$

Calcd. C: 59.98; H: 5.29; N: 13.99

Found C: 60.00; H: 5.56 N: 13.70

Example 186

In a sealed tube, a mixture of ethyl 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (100 mg) and isopropylamine (0.5 mL) in tetrahydrofuran (2 mL) was heated for 80 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of diisopropyl ether to give 4-(4-fluorophenyl)-N-isopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (96 mg).

m.p.: 122-123.5℃ (diisopropyl ether - n-hexane)

IR (KBr) : 3417, 1664, 1587, 1518 cm^{-1}

ESI/MS : 423$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.56 Hz), 1.37(6H, d, J=6.62 Hz), 4.25-4.31(1H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.75(1H, d, J=9.66 Hz),

6.95(1H, d, J=9.66 Hz), 7.08(1H, d, J=8.06 Hz), 7.13-7.18(2H, m), 7.51-7.56(2H, m)

Elemental Analysis for $C_{20}H_{21}FN_4O_2S$

Calcd. C: 59.98; H: 5.29; N: 13.99

Found C: 60.02; H: 5.40; N: 13.86

Example 187

In a sealed tube, a mixture of ethyl 4-(3-chlorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (203 mg) and isopropylamine (1 mL) in tetrahydrofuran (4 mL) was heated for 80 hours at 50-55℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of diisopropyl ether and n-hexane to give 4-(3- chlorophenyl)-N-isopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3- pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (177 mg).

m.p.: 105-106℃ (diisopropyl ether - n-hexane)

IR (KBr) : 1662, 1591, 1531 cm^{-1}

ESI/MS : 857 and 855$(2M+Na)^+$, 441 and 439$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.31(3H, d, J=6.61 Hz), 1.36(3H, d, J=6.64 Hz), 4.19-4.38(1H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.77(1H, d, J=9.66 Hz), 7.04(1H, d, J=9.66 Hz), 7.31(1H, d, J=8.38 Hz), 7.35-7.61(3H, m), 7.61-7.63(1H, m)

Elemental Analysis for $C_{20}H_{21}ClN_4O_2S$

Calcd. C: 57.62; H: 5.08; N: 13.44

Found C: 57.94; H: 5.31; N: 13.54

Example 188

In a sealed tube, a mixture of ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (164 mg) and cyclopropylamine (0.347 mL) in dioxane (0.5 mL) was heated for 40 hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-cyclopropyl-5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid

(81 mg).

m.p.: >250℃ (ethanol - diisopropyl ether)

IR (KBr) : 3267, 1680, 1651, 1591, 1552 cm^{-1}

ESI/MS : 361$(M+Na)^+$, 339$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 0.70-0.72(4H, m), 2.87-2.92(1H, m), 6.83(1H, d, J=9.92 Hz), 7.04(1H, d, J=9.92 Hz), 7.45-7.49(3H, m), 7.57-7.60(2H, m), 8.93(1H, d, J=4.80 Hz), 13.38(1H, br.s)

Elemental Analysis for $C_{17}H_{14}N_4O_2S$

Calcd. C: 60.34; H: 4.17; N: 16.56

Found C: 60.44; H: 4.22; N: 16.59

Example 189

In a sealed tube, a mixture of ethyl 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (171 mg) and cyclopropylamine (0.347 mL) in dioxane (0.5 mL) was heated for 40 hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-cyclopropyl-5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2- carboxamide as a solid (152 mg).

m.p.: 163-164℃ (ethanol - diisopropyl ether)

IR (KBr) : 1672, 1651 cm^{-1}

ESI/MS : 375$(M+Na)^+$, 353$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.69-0.72(2H, m), 0.87-0.93(2H, m), 2.91-2.95(1H, m), 3.84(3H, s), 6.72(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.35(1H, br.s), 7.43-7.47(3H, m), 7.48-7.52(2H, m)

Elemental Analysis for $C_{18}H_{16}N_4O_2S$

Calcd. C: 61.35; H: 4.58; N: 15.90

Found C: 61.35; H: 4.70; N: 15.83

Example 190

In a sealed tube, a mixture of ethyl 5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (178 mg) and cyclopropylamine (0.347 mL) in dioxane (0.5 mL) was heated for 40

hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-cyclopropyl-5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2- carboxamide as a solid (144mg).

m.p.: 144-145℃ (ethanol - diisopropyl ether)

IR (KBr) : 3286, 1668, 1653, 1591, 1527 cm^{-1}

ESI/MS : 389$(M+Na)^+$, 367$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.69-0.72(2H, m), 0.87-0.91(2H, m), 1.42(2H, t, J=7.20 Hz), 2.91-2.95(1H, m), 4.25(2H, q, J=7.20 Hz), 6.72(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.35(1H, br.s), 7.43-7.47(3H, m), 7.50-7.53(2H, m)

Elemental Analysis for $C_{19}H_{18}N_4O_2S$

Calcd. C: 62.28; H: 4.95; N: 15.29

Found C: 62.42; H: 5.18; N: 15.29

Example 191

In a sealed tube, a mixture of ethyl 5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (185 mg) and cyclopropylamine (0.347 mL) in dioxane (0.5 mL) was heated for 40 hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-cyclopropyl-5-(6-oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2- carboxamide as a solid (144 mg).

m.p.: 146-147℃ (ethanol - diisopropyl ether)

IR (KBr) : 3282, 1676, 1655, 1593, 1535 cm^{-1}

ESI/MS : 403$(M+Na)^+$, 381$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.69-0.71(2H, m), 0.88-0.91(2H, m), 1.00(3H, t, J=7.42 Hz), 1.84-1.90(2H, m), 2.90-2.96(1H, m), 4.16(2H, t, J=7.36 Hz), 6.72(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.34(1H, br.s), 7.43-7.47(3H, m), 7.49-7.53(2H, m)

Elemental Analysis for $C_{20}H_{20}N_4O_2S$

Calcd. C: 63.14; H: 5.30; N: 14.73

Found C: 63.26; H: 5.41; N: 14.71

Example 192

In a sealed tube, a mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and cyclopropylamine (0.075 mL) in dioxane (0.3 mL) was heated for 10 hours at 80-85℃. The mixture was poured into a mixture of water and chloroform. A separated organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) and crystallized from a mixture of ethanol and n-hexane to give N-cyclopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2- carboxamide as a solid (71 mg).

m.p.: 127-128℃ (ethanol - n-hexane)

IR (KBr) : 3228, 1666, 1643, 1590, 1533 cm^{-1}

ESI/MS : 783(2M+Na)$^+$, 403(M+Na)$^+$

^{1}H NMR ($CDCl_3$, δ) : 0.67-0.74(2H, m), 0.85-0.95(2H, m), 1.38(6H, d, J=6.62 Hz), 2.89-2.99(1H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.70(1H, d, J=9.70 Hz), 6.93(1H, d, J=9.70 Hz), 7.33(1H, d, J=2.68 Hz), 7.42-7.55(5H, m)

Elemental Analysis for $C_{20}H_{20}N_4O_2S$

Calcd. C: 63.14; H: 5.30; N: 14.73

Found C: 62.89; H: 5.26; N: 14.58

Example 193

In a sealed tube, a mixture of ethyl 5-(1-allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (184 mg) and cyclopropylamine (0.347 mL) in dioxane (0.5 mL) was heated for 40 hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-cyclopropyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (142 mg).

m.p.: 167.5-168.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3284, 1678, 1655, 1593, 1533 cm^{-1}

ESI/MS : 779($2M+Na)^+$, 401($M+Na)^+$, 379($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.67-0.72(2H, m), 0.87-0.93(2H, m), 2.90-2.96(1H, m), 4.78-4.80(2H, m), 5.28-5.36(2H, m), 5.99-6.07(1H, m), 6.74(1H, d, J=9.72 Hz), 6.94(1H, d, J=9.72 Hz), 7.34(1H, br.s), 7.42-7.47(3H, m), 7.49-7.53(2H, m)

Elemental Analysis for $C_{20}H_{18}N_4O_2S$

Calcd. C: 63.48; H: 4.79; N: 14.80

Found C: 63.29; H: 4.64; N: 14.74

Example 194

In a sealed tube, a mixture of ethyl 5-(1-benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (105 mg) and cyclopropylamine (0.174 mL) in dioxane (0.25 mL) was heated for 40 hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-cyclopropyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (84 mg).

m.p.: 151-152.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3298, 1674, 1657, 1591, 1527 cm^{-1}

ESI/MS : 879($2M+Na)^+$, 451($M+Na)^+$, 429($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.67-0.72(2H, m), 0.87-0.93(2H, m), 2.91-2.96(1H, m), 5.33(2H, s), 6.71(1H, d, J=9.72 Hz), 6.91(1H, d, J=9.72 Hz), 7.33-7.51(11H, m)

Elemental Analysis for $C_{24}H_{20}N_4O_2S$

Calcd. C: 67.27; H: 4.70; N: 13.07

Found C: 67.33; H: 4.74; N: 13.09

Example 195

In a sealed tube, a mixture of ethyl 5-[1-(2-methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-1,3-thiazole-2-carboxylate (96.8 mg) and cyclopropylamine (0.174 mL) in dioxane (0.25 mL) was

heated for 40 hours at 70-75℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give N-cyclopropyl-5-[1-(2-methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-1,3-thiazole-2-carboxamide as a solid (77 mg).

m.p.: 161-162.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3290, 1674, 1655, 1591, 1529 cm^{-1}

ESI/MS : 815($2M+Na)^+$, 419($M+Na)^+$, 397($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.69-0.72(2H, m), 0.87-0.91(2H, m), 2.91-2.95(1H, m), 3.40(3H, s), 3.83(2H, t, J=5.60 Hz), 4.40(2H, t, J=5.60 Hz), 6.73(1H, d, J=9.72 Hz), 6.93(1H, d, J=9.72 Hz), 7.34(1H, br.s), 7.44-7.47(3H, m), 7.50-7.53(2H, m)

Elemental Analysis for $C_{20}H_{20}N_4O_3S$

Calcd. C: 60.59; H: 5.08; N: 14.13

Found C: 60.74; H: 5.04; N: 14.22

Example 196

In a sealed tube, a mixture of ethyl 4-(2-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (202 mg) and cyclopropylamine (0.145 mL) in dioxane (0.3 mL) was heated for 12 hours at 80-85℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and n-hexane to give N-cyclopropyl-4-(2-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (117 mg).

m.p.: 133.5-135℃ (ethanol - n-hexane)

IR (KBr) : 3222, 1664, 1639, 1593, 1533 cm^{-1}

ESI/MS : 421($M+Na)^+$, 399($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.64-0.74(2H, m), 0.76-0.95(2H, m), 1.29(6H, d, J=6.58 Hz), 2.87-2.99(1H, m), 5.27(1H, 7-plet, J=6.58 Hz), 6.75(1H, d, J=9.57 Hz), 6.99(1H, d, J=9.57 Hz), 7.11-7.21(1H, m), 7.20-7.55(4H, m)

Elemental Analysis for $C_{20}H_{19}FN_4O_2S$

Calcd. C: 60.29; H: 4.81; N: 14.06

Found C: 60.57; H: 4.95; N: 14.03

Example 197

In a sealed tube, a mixture of ethyl 4-(3-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (201 mg) and cyclopropylamine (0.144 mL) in dioxane (0.3 mL) was heated for 12 hours at 80-85℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and n-hexane to give N-cyclopropyl-4-(3-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (160 mg).

m.p.: 145.5-147℃ (ethanol - n-hexane)

IR (KBr) : 3249, 1660, 1587 cm^{-1}

ESI/MS : 819$(2M+Na)^+$, 421$(M+Na)^+$, 399$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.66-0.75(2H, m), 0.86-0.97(2H, m), 1.37(6H, d, J=6.62 Hz), 2.89-2.99(1H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.76(1H, d, J=9.65 Hz), 6.98(1H, d, J=9.65 Hz), 7.10-7.47(5H, m)

Elemental Analysis for $C_{20}H_{19}FN_4O_2S \cdot 0.2H_2O$

Calcd. C: 59.75; H: 4.86; N: 13.94

Found C: 60.05; H: 5.12; N: 13.64

Example 198

In a sealed tube, a mixture of ethyl 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2- carboxylate (100 mg) and cyclopropylamine (0.072 mL) in dioxane (0.3 mL) was heated for 10 hours at 80-85℃. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) and crystallized from a mixture of ethanol and diisopropyl ether to give N-cyclopropyl-4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (78 mg).

m.p.: 157.-158℃ (ethanol - diisopropyl ether)

IR (KBr) : 3228, 1668, 1651, 1637, 1539 cm^{-1}

ESI/MS : 421$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 0.69-0.72(2H, m), 0.87-0.92(2H, m), 1.37(6H, d,

J=6.62 Hz), 2.92-2.95(1H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.74(1H, d, J=9.68 Hz), 6.94(1H, d, J=9.68 Hz), 7.12-7.17(2H, m), 7.31(1H, d, J=2.92 Hz), 7.49-7.53(2H, m)

Elemental Analysis for $C_{20}H_{19}FN_4O_2S$

Calcd. C: 60.29; H: 4.81; N: 14.06

Found C: 60.34; H: 4.72; N: 13.98

Example 199

In a sealed tube, a mixture of ethyl 4-(3-chlorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (203 mg) and cyclopropylamine (0.139 mL) in dioxane (0.3 mL) was heated for 12 hours at 80-85℃. The mixture was concentrated under reduced pressure to give a residue. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 4-(3-chlorophenyl)-N-cyclopropyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxamide as a solid (141 mg).

m.p.: 118.5-119.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3251, 1660, 1645, 1585 cm^{-1}

ESI/MS : 853 and 851$(2M+Na)^+$, 439 and 437$(M+Na)^+$, 415$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.66-0.76(2H, m), 0.86-0.97(2H, m), 1.36(6H, d, J=6.64 Hz), 2.98-2.99(1H, m), 5.31(1H, 7-plet, J=6.64 Hz), 6.77(1H, d, J=9.78 Hz), 6.99(1H, d, J=9.78 Hz), 7.32-7.59(4H, m), 7.58-7.60(1H, m)

Elemental Analysis for $C_{20}H_{19}ClN_4O_2S \cdot 0.2H_2O$

Calcd. C: 57.40; H: 4.67; N: 13.39

Found C: 57.47; H: 4.76; N: 13.30

Example 200

A mixture of ethyl 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (164 mg) and 2-pyridinylmethylamine (0.155 mL) in dioxane (0.5 mL) was heated for 40 hours at 90-95℃. Water (4 mL) and chloroform (4 mL) were added to the mixture to give a solid. The solid was collected by filtration, dried over phosphorous petoxide and crystallized from ethanol to give 5-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-

carboxamide as a solid (48 mg).

m.p.: 221-222.5℃ (ethanol)

IR (KBr) : 3226, 1674, 1595, 1529 cm^{-1}

ESI/MS : 412$(M+Na)^+$, 390$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 4.60(2H, d, J=6.06 Hz), 6.84(1H, d, J=9.80 Hz), 7.08(1H, d, J=9.80 Hz), 7.25-7.38(2H, m), 7.46-7.52(3H, m), 7.60-7.66(2H, m), 7.72-7.81(1H, m), 8.50-8.54(1H, m), 9.47(1H, t, J=6.06 Hz), 13.37(1H, br.s)

Elemental Analysis for $C_{20}H_{15}N_5O_2S$

Calcd. C: 61.68; H: 3.88; N: 17.98

Found C: 61.36; H: 4.05; N: 17.79

Example 201

A mixture of ethyl 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (171 mg) and 2-pyridinylmethylamine (0.155 mL) in dioxane (0.5 mL) was heated for 40 hours at 90-95℃. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 10 : 90, v/v) to give 5-(1-methyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide as a solid (189 mg).

m.p.: 189-190.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3369, 1674, 1589, 1510 cm^{-1}

ESI/MS : 829$(2M+Na)^+$, 426$(M+Na)^+$, 404$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 3.85(3H, s), 4.79(2H, d, J=5.60 Hz), 6.73(1H, d, J=9.65 Hz), 6.96(1H, d, J=9.65 Hz), 7.22-7.27(1H, m), 7.32-7.74(7H, m), 8.28(1H, br.t, J=5.40 Hz), 8.59(1H, d, J=4.26 Hz)

Elemental Analysis for $C_{21}H_{17}N_5O_2S$

Calcd. C: 62.52; H: 4.25; N: 17.36

Found C: 62.44; H: 4.35; N: 17.26

Example 202

5-(1-Ethyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner

similar to Example 201.

m.p.: 169-170.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 1678, 1593, 1527 cm^{-1}

ESI/MS : 440$(M+Na)^+$, 418$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.43(3H, t, J=7.18 Hz), 4.25(2H, q, J=7.18 Hz), 4.79(2H, d, J=5.62 Hz), 6.72(1H, d, J=9.70 Hz), 6.96(1H, d, J=9.70 Hz), 7.22-7.74(8H, m), 8.27(1H, br.t, J=5.37 Hz), 8.59(1H, d, J=4.34 Hz)

Elemental Analysis for $C_{22}H_{19}N_5O_2S$

Calcd. C: 63.29; H: 4.59; N: 16.78

Found C: 63.15; H: 4.66; N: 16.63

Example 203

5-(6-Oxo-1-propyl-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 134-135.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3386, 1668, 1587, 1512 cm^{-1}

ESI/MS : 885$(2M+Na)^+$, 454$(M+Na)^+$, 432$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.00(3H, t, J=7.38 Hz), 1.78-1.97(2H, m), 4.16(2H, t, J=7.32 Hz), 4.79(2H, d, J=5.62 Hz), 6.72(1H, d, J=9.68 Hz), 6.96(1H, d, J=9.68 Hz), 7.21-7.74(8H, m), 8.27(1H, br.t, J=5.49 Hz), 8.59(1H, d, J=4.50 Hz)

Elemental Analysis for $C_{23}H_{21}N_5O_2S$

Calcd. C: 64.02; H: 4.91; N: 16.23

Found C: 64.00; H: 4.99; N: 16.06

Example 204

5-(1-Allyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 117-118℃ (acetone - n-hexane)

IR (KBr) : 1680, 1658, 1591, 1514 cm^{-1}

ESI/MS : 881$(2M+Na)^+$, 452$(M+Na)^+$, 430$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 4.77-4.82(4H, m), 5.28-5.38(2H, m), 5.91-6.15(1H,

m), 6.74(1H, d, J=9.60 Hz), 6.97(1H, d, J=9.60 Hz), 7.23-7.74(8H, m), 8.27(1H, br.t, J=5.56 Hz), 8.59(1H, d, J=4.92 Hz)

Elemental Analysis for $C_{23}H_{19}N_5O_2S$

Calcd. C: 64.32; H: 4.46; N: 16.31

Found C: 64.19; H: 4.47; N: 16.13

Example 205

5-(1-Benzyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 172.5-173.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3346, 1678, 1589, 1527 cm^{-1}

ESI/MS : 981$(2M+Na)^+$, 502$(M+Na)^+$, 480$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 4.79(2H, d, J=5.68 Hz), 5.34(2H, s), 6.72(1H, d, J=9.68 Hz), 6.93(1H, d, J=9.68 Hz), 7.26-7.73(13H, m), 8.27(1H, br.t, J=8.27 Hz), 8.58(1H, d, J=4.32 Hz)

Elemental Analysis for $C_{27}H_{21}N_5O_2S \cdot 0.2H_2O$

Calcd. C: 67.12; H: 4.46; N: 14.49

Found C: 67.19; H: 4.40; N: 14.49

Example 206

5-[1-(2-Methoxyethyl)-6-oxo-1,6-dihydro-3-pyridazinyl]-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 168-169.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3379, 1660, 1589, 1522 cm^{-1}

ESI/MS : 917$(2M+Na)^+$, 470$(M+Na)^+$, 448$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 3.40(3H, s), 3.83(2H, t, J=5.58 Hz), 4.40(2H, t, J=5.58 Hz), 4.79(2H, d, J=5.64 Hz), 6.73(1H, d, J=9.62 Hz), 6.96(1H, d, J=9.62 Hz), 7.21-7.74(8H, m), 8.27(1H, br.t, J=5.35 Hz), 8.59(1H, d, J=5.00 Hz)

Elemental Analysis for $C_{23}H_{21}N_5O_3S$

Calcd. C: 61.73; H: 4.73; N: 15.65

Found C: 61.59; H: 4.80; N: 15.44

Example 207

4-(2-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 190-191℃ (ethanol)

IR (KBr) : 3354, 1668, 1595, 1513 cm^{-1}

ESI/MS : 921$(2M+Na)^+$, 472$(M+Na)^+$, 450$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.30(6H, d, J=6.62 Hz), 4.79(2H, d, J=5.60 Hz), 5.28(1H, 7-plet, J=6.62 Hz), 6.76(1H, d, J=9.75 Hz), 7.01(1H, d, J=9.75 Hz), 7.09-7.80(7H, m), 8.18-8.24(1H, m), 8.56-8.60(1H, m)

Elemental Analysis for $C_{23}H_{20}FN_5O_2S$

Calcd. C: 61.46; H: 4.48; N: 15.58

Found C: 61.40; H: 4.53; N: 15.47

Example 208

4-(3-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 188-189.5℃ (ethanol)

IR (KBr) : 3384, 1668, 1587, 1512 cm^{-1}

ESI/MS : 921$(2M+Na)^+$, 472$(M+Na)^+$, 450$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.62 Hz), 4.80(2H, d, J=5.56 Hz), 5.32(1H, 7-plet, J=6.62 Hz), 6.77(1H, d, J=9.74 Hz), 7.01(1H, d, J=9.74 Hz), 7.15-7.43(H, m), 7.65-7.76(1H, m), 8.25-8.31(1H, m), 8.59-8.62(1H, m)

Elemental Analysis for $C_{23}H_{20}FN_5O_2S$

Calcd. C: 61.46; H: 4.48; N: 15.58

Found C: 61.42; H: 4.55; N: 15.49

Example 209

4-(3-Chlorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 201.

m.p.: 168-169.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3384, 1668, 1587, 1514 cm^{-1}

ESI/MS : 955 and 953$(2M+Na)^+$, 490 and 488$(M+Na)^+$, 468 and 466$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.60 Hz), 4.80(2H, d, J=5.56 Hz), 5.32(1H, 7-plet, J=6.60 Hz), 6.78(1H, d, J=9.78 Hz), 7.01(1H, d, J=9.78 Hz), 7.23-7.27(1H, m), 7.33-7.43(5H, m), 7.61-7.74(2H, m), 8.24-8.30(1H, m), 8.59-8.62(1H, m)

Elemental Analysis for $C_{23}H_{20}ClN_5O_2S$

Calcd. C: 59.29; H: 4.33; N: 15.03

Found C: 59.38; H: 4.38; N: 14.98

Example 210

A mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and 2-pyridinylmethylamine (0.112 mL) in dioxane (0.3 mL) was heated for 10 hours at 80-85℃. To the mixture was added water (3 mL) to obtain a solid. The solid was collected by filtration, dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a solid. The solid was crystallized from a mixture of ethanol and diisopropyl ether to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide as a solid (90 mg).

m.p.: 176.5-177.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3384, 1666, 1589, 1513 cm^{-1}

ESI/MS : 885$(2M+Na)^+$, 454$(M+Na)^+$, 432$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.23(6H, d, J=6.62 Hz), 4.79(2H, d, J=5.50 Hz), 5.33(1H, 7-plet, J=6.62 Hz), 6.71(1H, d, J=9.70 Hz), 6.96(1H, d, J=9.70 Hz), 7.20-7.24(1H, m), 7.35(1H, d, J=7.84 Hz), 7.44-7.50(3H, m), 7.54-7.57(2H, m), 7.66-7.69(1H, m), 8.26(1H, t, J=5.50 Hz), 8.59(1H, d, J=4.84 Hz)

Elemental Analysis for $C_{23}H_{21}N_5O_2S$

Calcd. C: 64.02; H: 4.91; N: 16.23

Found C: 63.81; H: 4.86; N: 16.08

Example 211

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(2-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 210.

m.p.: 203.5-205℃ (ethanol - diisopropyl ether)

IR (KBr) : 3383, 1668, 1587, 1514 cm^{-1}

ESI/MS : 472$(M+Na)^+$, 450$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.64 Hz), 4.79(2H, d, J=5.56 Hz), 5.32(1H, 7-plet, J=6.64 Hz), 6.75(1H, d, J=9.68 Hz), 6.98(1H, d, J=9.68 Hz), 7.11-7.18(2H, m), 7.23(1H, dd, J=5.02,6.79 Hz), 7.35(1H, d, J=7.82 Hz), 7.52-7.58(2H, m), 7.69(1H, dt, J=1.78,7.68 Hz), 8.27(1H, t, J=5.56 Hz), 8.58-8.61(1H, m)

Elemental Analysis for $C_{23}H_{20}FN_5O_2S$

Calcd. C: 61.46; H: 4.48; N: 15.58

Found C: 61.43; H: 4.58; N: 15.42

Example 212

A mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (500 mg) and potassium tert-butoxide (152 mg) in methylformamide (5 mL) was heated for 5 hours at 95-100℃. Water (50 mL) and 1N-hydrochloric acid (1.35 mL) were added to the reaction mixture. The mixture was extracted with chloroform (20 mL x 5). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-methyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (143 mg).

m.p.: 165-167.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3396, 1666, 1589, 1531 cm^{-1}

ESI/MS : 377$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 3.05(3H, d, J=5.10 Hz), 5.31(1H, 7-plet, J=6.60 Hz), 6.71(1H, d, J=9.72 Hz), 6.95(1H, d, J=9.72

Hz), 7.25-7.35(1H, m), 7.43-7.56(5H, m)
Elemental Analysis for $C_{18}H_{18}N_4O_2S$
Calcd. C: 61.00; H: 5.12; N: 15.81
Found C: 60.91; H: 5.23; N: 15.75

Example 213

To a solution of 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-methyl-4-phenyl-1,3-thiazole-2-carboxamide (68 mg) in dimethylformamide (0.2 mL) was added sodium hydride (60 % in oil) (8.4 mg), and the mixture was stirred for 30 minutes at 50-55℃. Iodomethane (0.0241 mL) was added to the mixture, and the mixture was stirred at ambient temperature for 18 hours. Water (3 mL) was added to the mixture. The mixture was extracted with ethyl acetate (2 mL x 4). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N,N-dimethyl-4-phenyl-1,3-thiazole-2-carboxamide as a solid (40 mg).
m.p.: 141-144℃ (diisopropyl ether)
IR (KBr) : 1664, 1626, 1587 cm^{-1}
ESI/MS : 759($2M+Na)^+$, 391($M+Na)^+$, 369($M+H)^+$
^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.63 Hz), 3.18(3H, s), 3.65(3H, s), 5.31(1H, 7-plet, J=6.63 Hz), 6.72(1H, d, J=9.70 Hz), 6.99(1H, d, J=9.70 Hz), 7.41-7.47(3H, m), 7.49-7.57(2H, m)
Elemental Analysis for $C_{19}H_{20}N_4O_2S$
Calcd. C: 61.94; H: 5.47; N: 15.21
Found C: 61.88; H: 5.60; N: 15.13

Example 214

In a sealed tube, a mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and ethylamine (0.406 mL) in tetrahydrofuran (2 mL) was heated at 50-55℃ for 70 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by preparative

TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give N-ethyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (84 mg).

m.p.: 172-174℃ (ethanol - diisopropyl ether)

IR (KBr) : 3305, 1670, 1658, 1539 cm^{-1}

ESI/MS : 759($2M+Na)^+$, 391($M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.28(3H, t, J=7.27 Hz), 1.38(6H, d, J=6.60 Hz), 3.45-3.60(2H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.71(1H, d, J=9.78 Hz), 6.95(1H, d, J=9.78 Hz), 7.25-7.35(1H, m), 7.42-7.57(5H, m)

Elemental Analysis for $C_{19}H_{20}N_4O_2S$

Calcd. C: 61.94; H: 5.47; N: 15.21

Found C: 62.07; H: 5.57; N: 15.20

Example 215

A mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and butylamine (0.108 mL) in dioxane (0.3 mL) was heated for 10 hours at 80-85℃. Water (2 mL) and 1N-hydrochloric acid (0.5 mL) were added to the mixture. The mixture was extracted with chloroform (3 mL), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give N-butyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (40 mg).

m.p.: 147.5-148.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3294, 1672, 1537 cm^{-1}

ESI/MS : 815($2M+Na)^+$, 419($M+Na)^+$, 397($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 0.96(3H, t, J=7.22 Hz), 1.33-1.67(4H, m), 1.38(6H, d, J=6.66 Hz), 3.42-3.53(2H, m), 5.31(1H, 7-plet), 6.70(1H, d, J=9.58 Hz), 6.94(1H, d, J=9.58 Hz), 7.26-7.32(1H, m), 7.43-7.57(5H, m)

Elemental Analysis for $C_{21}H_{24}N_4O_2S \cdot 0.1H_2O$

Calcd. C: 63.33; H: 6.12; N: 14.07

Found C: 63.27; H: 6.05; N: 14.02

Example 216

5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(2-methoxyethyl)-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 215.

m.p.: 131-132.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3419, 1674, 1589, 1527 cm^{-1}

ESI/MS : 819$(2M+Na)^+$, 421$(M+Na)^+$, 399$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.62 Hz), 3.39(3H, s), 3.58(2H, t, J=4.96 Hz), 3.65-3.70(2H, m), 5.31(1H, 7-plet, J=6.62 Hz), 6.71(1H, d, J=9.70 Hz), 6.94(1H, d, J=9.70 Hz), 7.44-7.47(3H, m), 7.52-7.60(3H, m)

Elemental Analysis for $C_{20}H_{22}N_4O_3S$

Calcd. C: 60.28; H: 5.56; N: 14.06

Found C: 60.11; H: 5.47; N: 14.02

Example 217

N-[2-(Acetylamino)ethyl]-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 215.

m.p.: 170-171.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3294, 1657, 1585, 1533 cm^{-1}

ESI/MS : 873$(2M+Na)^+$, 448$(M+Na)^+$, 426$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.62 Hz), 2.00(3H, s), 3.47-3.56(2H, m), 3.58-3.68(2H, m), 5.32(1H, 7-plet, J=6.62 Hz), 6.16(1H, br.s), 6.71(1H, d, J=9.63 Hz), 6.95(1H, d, J=9.63 Hz), 7.43-7.57(5H, m), 7.68(1H, t, J=5.78 Hz)

Elemental Analysis for $C_{21}H_{23}N_5O_3S$

Calcd. C: 59.28; H: 5.45; N: 16.46

Found C: 58.83; H: 5.36; N: 16.28

Example 218

2-Isopropyl-6-[4-phenyl-2-(1-piperidinylcarbonyl)-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 215.

m.p.: 111-112℃ (n-hexane)

IR (KBr) : 1670, 1618, 1589 cm^{-1}

ESI/MS : 839($2M+Na)^+$, 431($M+Na)^+$, 409($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.64 Hz), 1.71(6H, br.s), 3.75(2H, br.s), 4.29(2H, br.s), 5.31(1H, 7-plet, J=6.64 Hz), 6.71(1H, d, J=9.68 Hz), 6.98(1H, d, J=9.68 Hz), 7.41-7.45(3H, m), 7.52-7.55(2H, m)

Elemental Analysis for $C_{22}H_{24}N_4O_2S \cdot 0.1H_2O$

Calcd. C: 64.40; H: 5.94; N: 13.65

Found C: 64.38; H: 5.82; N: 13.61

Example 219

6-{2-[(4-Acetyl-1-piperazinyl)carbonyl]-4-phenyl-1,3-thiazol-5-yl}-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 215.

m.p.: 78-82℃ (n-hexane)

IR (KBr) : 1662, 1624, 1589 cm^{-1}

ESI/MS : 474($M+Na)^+$, 452($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.62 Hz), 2.15(3H, s), 3.55-3.90(6H, m), 4.40-4.65(2H, m), 5.32(1H, 7-plet, J=6.62 Hz), 6.73(1H, d, J=9.68 Hz), 6.98(1H, d, J=9.68 Hz), 7.42-7.55(5H, m)

Elemental Analysis for $C_{23}H_{25}N_5O_3S \cdot 0.5H_2O$

Calcd. C: 59.98; H: 5.69; N: 15.21

Found C: 60.14; H: 5.65; N: 14.95

Example 220

N-Benzyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 215.

m.p.: 186-187℃ (ethanol - diisopropyl ether)

IR (KBr) : 3344, 1660, 1587, 1529 cm^{-1}

ESI/MS : 883($2M+Na)^+$, 453($M+Na)^+$, 431($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.63 Hz), 4.67(2H, d, J=6.14 Hz), 5.31(1H, 7-plet, J=6.63 Hz), 6.71(1H, d, J=9.68 Hz), 6.94(1H, d, J=9.668 Hz), 7.30-7.60(11H, m)

Elemental Analysis for $C_{24}H_{22}N_4O_2S \cdot 0.1H_2O$

Calcd. C: 66.68; H: 5.18; N: 12.96

Found C: 66.64; H: 5.13; N: 12.93

Example 221

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-[(5-methyl-2-pyrazinyl)methyl]-1,3-thiazole-2- carboxamide was obtained in a manner similar to Example 215.

m.p.: 187.5-188.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 1670, 1520 cm^{-1}

ESI/MS : 487$(M+Na)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.62 Hz), 2.57(3H, s), 4.79(2H, d, J=5.76 Hz), 5.31(1H, 7-plet, J=6.62 Hz), 6.75(1H, d, J=9.68 Hz), 6.97(1H, d, J=9.68 Hz), 7.12-7.17(2H, m), 7.51-7.56(2H, m), 8.06(1H, t, J=5.76 Hz), 8.43(1H, s), 8.56(1H, s)

Elemental Analysis for $C_{23}H_{21}FN_6O_2S$

Calcd. C: 59.47; H: 4.56; N: 18.09

Found C: 59.36; H: 4.54; N: 18.00

Example 222

A mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg), 2-aminoacetamide hydrochloride (120 mg) and triethylamine (0.151 mL) in dioxane (0.3 mL) was heated for 10 hours at 80-85℃. To the reaction mixture, water (2 mL) and 1N-hydrochloric acid (0.5 mL) were added to give a precipitate. The precipitate was collected by filtration, dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was crystallized from ethanol to give N-(2-amino-2-oxoethyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide as a solid (60 mg).

m.p.: 247.5-249℃ (ethanol)

IR (KBr) : 3392, 3199, 1666, 1587 cm^{-1}

ESI/MS : 817$(2M+Na)^+$, 420$(M+Na)^+$

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.66 Hz), 3.86(2H, d, J=5.95 Hz), 5.13(1H, 7-plet, J=6.66 Hz), 6.89(1H, d, J=9.62 Hz), 7.12(1H, br.s),

7.16(1H, d, J=9.62 Hz), 7.46-7.63(6H, m), 8.87(1H, t, J=5.95 Hz)
Elemental Analysis for $C_{19}H_{19}N_5O_3S$
Calcd. C: 57.42; H: 4.82; N: 17.62
Found C: 57.54; H: 4.90; N: 17.25

Example 223

N-[2-(Dimethylamino)ethyl]-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 222.
m.p.: 151-152.5℃ (ethanol - diisopropyl ether)
IR (KBr) : 3408, 1668, 1587, 1514 cm^{-1}
ESI/MS : 434$(M+Na)^+$, 412$(M+H)^+$
^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 2.53(2H, t, J=6.11 Hz), 3.51-3.61(2H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.70(1H, d, J=9.70 Hz), 6.94(1H, d, J=9.70 Hz), 7.43-7.62(6H, m)
Elemental Analysis for $C_{21}H_{25}N_5O_2S$
Calcd. C: 61.29; H: 6.12; N: 17.02
Found C: 61.10; H: 6.03; N: 16.84

Example 224

5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-[2-(4-morpholinyl)-ethyl]-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 222.
m.p.: 196.5-197.5℃ (ethanol)
IR (KBr) : 3413, 1670, 1587, 1512 cm^{-1}
ESI/MS : 929$(2M+Na)^+$, 476$(M+Na)^+$, 454$(M+H)^+$
^1H NMR ($CDCl_3$, δ) : H1.37(6H, d, J=6.60 Hz), 2.49-2.54(4H, m), 2.61(2H, t, J=6.19 Hz), 3.54-3.64(2H, m), 3.70-376(4H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.71(1H, d, J=9.60 Hz), 6.96(1H, d, J=9.60 Hz), 7.43-7.58(5H, m), 7.68(1H, t, J=5.27 Hz)
Elemental Analysis for $C_{23}H_{27}N_5O_3S$
Calcd. C: 60.91; H: 6.00; N: 15.44
Found C: 60.67; H: 5.90; N: 15.19

Example 225

N-Cyclohexyl-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 222.

m.p.: 225-226℃ (ethanol - diisopropyl ether)

IR (KBr) : 3307, 1670, 1597, 1531 cm^{-1}

ESI/MS : 867$(2M+Na)^+$, 445$(M+Na)^+$, 423$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.20-1.47(5H, m), 1.38(6H, d, J=6.60 Hz), 1.60-1.80(3H, m), 2.01-2.06(2H, m), 3.91-4.01(1H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.70(1H, d, J=9.66 Hz), 6.93(1H, d, J=9.66 Hz), 7.17(1H, br.s), 7.44-7.47(3H, m), 7.52-7.56(2H, m)

Elemental Analysis for $C_{23}H_{26}N_4O_2S \cdot 0.2H_2O$

Calcd. C: 64.83; H: 6.24; N: 13.15

Found C: 64.79; H: 6.11; N: 13.15

Example 226

2-Isopropyl-6-[4-phenyl-2-(1-pyrrolidinylcarbonyl)-1,3- thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 222.

m.p.: 169-170.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 1666, 1620, 1591 cm^{-1}

ESI/MS : 811$(2M+Na)^+$, 417$(M+Na)^+$, 395$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.62 Hz), 1.90-1.97(2H, m), 1.99-2.06(2H, m), 3.72(2H, t, J=6.85 Hz), 4.17(2H, t, J=6.85 Hz), 5.31(1H, 7-plet, J=6.62 Hz), 6.72(1H, d, J=9.68 Hz), 6.99(1H, d, J=9.68 Hz), 7.41-7.45(3H, m), 7.52-7.56(2H, m)

Elemental Analysis for $C_{21}H_{22}N_4O_2S$

Calcd. C: 63.94; H: 5.62; N: 14.20

Found C: 63.67; H: 5.52; N: 14.19

Example 227

2-Isopropyl-6-[2-(4-morpholinylcarbonyl)-4-phenyl-1,3-thiazol-5-yl]-3(2H)-pyridazinone was obtained in a manner similar to Example 222.

m.p.: 161.5-162.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 1664, 1624, 1585 cm^{-1}

ESI/MS : 843($2M+Na)^+$, 433($M+Na)^+$, 411($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 3.70-3.85(6H, m), 4.48-4.54(2H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.72(1H, d, J=9.58 Hz), 6.97(1H, d, J=9.58 Hz), 7.40-7.55(5H, m)

Elemental Analysis for $C_{21}H_{22}N_4O_3S$

Calcd. C: 61.45; H: 5.40; N: 13.65

Found C: 61.18; H: 5.30; N: 13.62

Example 228

2-Isopropyl-6-{2-[(4-methyl-1-piperazinyl)carbonyl]-4-phenyl-1,3-thiazol-5-yl}-3(2H)-pyridazinone was obtained in a manner similar to Example 222.

m.p.: 155-156.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 1668, 1628, 1589 cm^{-1}

ESI/MS : 869($2M+Na)^+$, 446($M+Na)^+$, 424($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.58 Hz), 2.34(3H, s), 2.48-2.54(4H, m), 3.82-3.86(2H, m), 4.45-4.49(2H, m), 5.31(1H, 7-plet, J=6.58 Hz), 6.72(1H, d, J=9.80 Hz), 6.97(1H, d, J=9.80 Hz), 7.41-7.56(5H, m)

Elemental Analysis for $C_{22}H_{25}N_5O_2S \cdot 0.1H_2O$

Calcd. C: 62.13; H: 5.97; N: 16.47

Found C: 62.03; H: 5.82; N: 16.47

Example 229

6-{2-[(4-Benzyl-1-piperazinyl)carbonyl]-4-phenyl-1,3- thiazol-5-yl}-2-isopropyl-3(2H)-pyridazinone was obtained in a manner similar to Example 222.

m.p.: 181-182℃ (ethanol)

IR (KBr) : 1666, 1624, 1587 cm^{-1}

ESI/MS : 522($M+Na)^+$, 500($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.60 Hz), 2.51-2.59(4H, m), 3.55(2H, s), 3.82-3.86(2H, m), 4.41-4.48(2H, m), 5.31(1H, 7-plet), 6.71(1H, d, J=9.62 Hz), 6.97(1H, d, J=9.62 Hz), 7.26-7.54(10H, m)

Elemental Analysis for $C_{28}H_{29}N_5O_2S \cdot 0.2H_2O$

Calcd. C: 66.83; H: 5.89; N: 13.92

Found C: 66.89; H: 5.73; N: 14.03

Example 230

5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(2-phenylethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 222.

m.p.: 115-116℃ (ethanol - diisopropyl ether)

IR (KBr) : 3361, 1660, 1587, 1531 cm^{-1}

ESI/MS : 911$(2M+Na)^+$, 467$(M+Na)^+$, 445$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.58 Hz), 2.96(2H, t, J=7.24 Hz), 3.67-3.79(2H, m), 5.31(1H, 7-plet, J=6.58 Hz), 6.70(1H, d, J=9.76 Hz), 6.95(1H, d, J=9.76 Hz), 7.23-7.52(11H, m)

Elemental Analysis for $C_{25}H_{24}N_4O_2S$

Calcd. C: 67.55; H: 5.44; N: 12.60

Found C: 76.32; H: 5.38; N: 12.55

Example 231

Under nitrogen atmosphere, a mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and 1-phenylpiperazine (0.165 mL) was heated for 18 hours at 120-125℃. The mixture was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give 2-isopropyl-6-{4-phenyl-2-[(4-phenyl-1-piperazinyl)carbonyl]-1,3-thiazol-5-yl}-3(2H)-pyridazinone as a solid (91 mg).

m.p.: 163.5-165℃ (ethanol)

IR (KBr) : 1664, 1625, 1591 cm^{-1}

ESI/MS : 508$(M+Na)^+$, 486$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 3.31(4H, br.s), 3.99(2H, br.s), 4.64(2H, br.s), 5.32(1H, 7-plet, J=6.60 Hz), 6.73(1H, d, J=9.70 Hz), 6.91-7.01(4H, m), 7.26-7.34(2H, m), 7.43-7.57(5H, m)

Elemental Analysis for $C_{27}H_{27}N_5O_2S \cdot 0.2H_2O$

Calcd. C: 66.29; H: 5.65; N: 14.32

Found C: 66.25; H: 5.52; N: 14.37

Example 232

A mixture of ethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carboxylate (100 mg) and 3-pyridinylmethylamine (0.111 mL) in dioxane (0.3 mL) was heated for 20 hours at 100-105℃. The mixture was concentrated under reduced pressure and purified by a column chromatography on silica gel (n-hexane : ethyl acetate = 20 : 80, v/v) to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(3-pyridinylmethyl)-1,3-thiazole-2-carboxamide as a solid (82 mg).

m.p.: 92.5-194℃ (ethanol - diisopropyl ether)

IR (KBr) : 1670, 1589 cm^{-1}

ESI/MS : 885$(2M+Na)^+$, 454$(M+Na)^+$, 432$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.60 Hz), 4.68(2H, d, J=6.26 Hz), 5.31(1H, 7-plet, J=6.60 Hz), 6.71(1H, d, J=9.66 Hz), 6.95(1H, d, J=9.66 Hz), 7.26-7.32(1H, m), 7.42-7.54(5H, m), 7.68-7.76(2H, m), 8.56(1H, dd, J=1.58,4.80 Hz), 8.63(1H, d, J=2.06 Hz)

Elemental Analysis for $C_{23}H_{21}N_5O_2S$

Calcd. C: 64.02; H: 4.91; N: 16.23

Found C: 63.90; H: 4.82; N: 16.15

Example 233

5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-(4-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 232.

m.p.: 192-193℃ (ethanol - diisopropyl ether)

IR (KBr) : 1670, 1589 cm^{-1}

ESI/MS : 454$(M+Na)^+$, 432$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.60 Hz), 4.68(2H, d, J=6.32 Hz), 5.32(1H, 7-plet, J=6.60 Hz), 6.72(1H, d, J=9.72 Hz), 6.95(1H, d, J=9.72 Hz), 7.26-7.30(2H, m), 7.43-7.56(5H, m), 7.74(1H, t, J=6.32 Hz), 8.57-8.61(2H, m)

Elemental Analysis for $C_{23}H_{21}N_5O_2S$

Calcd. C: 64.02; H: 4.91; N: 16.23

Found C: 63.74; H: 4.82; N: 16.10

Example 234

5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-N-[2-(2-pyridinyl)ethyl]-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 232.

m.p.: 144-147℃ (ethanol - diisopropyl ether)

IR (KBr) : 1666, 1587, 1520 cm^{-1}

ESI/MS : 913($2M+Na)^+$, 468($M+Na)^+$, 446($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 3.13(2H, t, J=6.54 Hz), 3.85-3.96(2H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.71(1H, d, J=9.64 Hz), 6.96(1H, d, J=9.64 Hz), 7.17-7.26(2H, m), 7.42-7.64(6H, m), 8.07(1H, t, J=5.88 Hz), 8.55-8.58(1H, m)

Elemental Analysis for $C_{24}H_{23}N_5O_2S$

Calcd. C: 64.70; H: 5.20; N: 15.72

Found C: 64.56; H: 5.15; N: 15.54

Example 235

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(3-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 232.

m.p.: 202-204℃ (ethanol - diisopropyl ether)

IR (KBr) : 1668, 1589 cm^{-1}

ESI/MS : 921($2M+Na)^+$, 472($M+Na)^+$, 450($M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 4.69(2H, d, J=6.28 Hz), 5.32(1H, 7-plet, J=6.60 Hz), 6.75(1H, d, J=9.66 Hz), 6.96(1H, d, J=9.66 Hz), 7.09-7.18(2H, m), 7.26-7.33(1H, m), 7.47-7.55(2H, m), 7.64-7.75(2H, m), 8.57(1H, dd, J=1.56,4.80 Hz), 8.64(1H, d, J=2.08 Hz)

Elemental Analysis for $C_{23}H_{20}FN_5O_2S$

Calcd. C: 61.46; H: 4.48; N: 15.58

Found C: 61.24; H: 4.41; N: 15.45

Example 236

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-(4-pyridinylmethyl)-1,3-thiazole-2-carboxamide was obtained in a

manner similar to Example 232.

m.p.: 155-157℃ (acetone - diisopropyl ether)

IR (KBr) : 1668, 1589 cm^{-1}

ESI/MS : 448$(M-1)^-$

^1H NMR ($CDCl_3$, δ) : 1.38(6H, d, J=6.60 Hz), 4.68(2H, d, J=6.40 Hz), 5.32(1H, 7-plet, J=6.60 Hz), 6.76(1H, d, J=9.69 Hz), 6.97(1H, d, J=9.69 Hz), 7.10-7.19(2H, m), 7.26-7.30(2H, m), 7.48-7.56(2H, m), 7.70(1H, t, J=6.40 Hz), 8.59(2H, d, J=5.74 Hz)

Elemental Analysis for $C_{23}H_{20}FN_5O_2S \cdot 0.1H_2O$

Calcd. C: 61.21; H: 4.51; N: 15.52

Found C: 61.41; H: 4.55; N: 15.10

Example 237

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-[2-(2-pyridinyl)ethyl]-1,3-thiazole-2-carboxamide was obtained in a manner similar to Example 232.

m.p.: 144-145℃ (acetone - diisopropyl ether)

IR (KBr) : 1670, 1589 cm^{-1}

ESI/MS : 486$(M+Na)^+$, 464$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.60 Hz), 3.13(2H, d, J=6.52 Hz), 3.85-3.96(2H, m), 5.31(1H, 7-plet, J=6.60 Hz), 6.75(1H, d, J=9.64 Hz), 6.97(1H, d, J=9.64 Hz), 7.09-7.24(4H, m), 7.49-7.64(3H, m), 8.10(1H, t, J=5.77 Hz), 8.54-8.58(1H, m)

Elemental Analysis for $C_{24}H_{22}FN_5O_2S \cdot H_2O$

Calcd. C: 59.86; H: 5.02; N: 14.54

Found C: 59.84; H: 5.06; N: 14.14

Example 238

In a sealed tube, a mixture of ethyl 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-1,3-thiazole-2-carboxylate (150 mg), O-methylhydroxylamine hydrochloride (162 mg) and potassium tert-butoxide (217 mg) in methanol (2 mL) was heatedfor 10 hours at 70-75℃. Water (9 ml) was added to the mixture to give a solid. The solid was collected by filtration, dissolved in chloroform,

dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a preparative TLC on silica gel (n-hexane : ethyl acetate = 50 : 50, v/v) to give 4-(4-fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N-methoxy-1,3-thiazole-2-carboxamide as a solid (32 mg).

m.p.: 164.5-166.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3421, 1722, 1668, 1587 cm^{-1}

ESI/MS : 396$(M+Na-15)^+$, 374$(M-14)^+$

^1H NMR ($CDCl_3$, δ) : 1.39(6H, d, J=6.62 Hz), 4.05(3H, s), 5.32(1H, 7-plet, J=6.62 Hz), 6.75(1H, d, J=9.72 Hz), 6.97(1H, d, J=9.72 Hz), 7.11-7.16(1H, m), 7.52-7.57(1H, m)

Example 239

4-(4-Fluorophenyl)-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-N',N'-dimethyl-1,3-thiazole-2-carbohydrazide was obtained in a manner similar to Example 238.

m.p.: 169-170.5℃ (ethanol - diisopropyl ether)

IR (KBr) : 3444, 1668 cm^{-1}

ESI/MS : 825$(2M+Na)^+$, 424$(M+Na)^+$, 402$(M+H)^+$

^1H NMR ($CDCl_3$, δ) : 1.37(6H, d, J=6.61 Hz), 2.74(6H, s), 5.31(1H, 7-plet, J=6.61 Hz), 6.75(1H, d, J=9.68 Hz), 6.95(1H, d, J=9.68 Hz), 7.13-7.19(2H, m), 7.51-7.55(2H, m), 7.96(1H, s)

Elemental Analysis for $C_{19}H_{20}FN_5O_2S$

Calcd. C: 56.85; H: 5.02; N: 17.44

Found C: 56.98; H: 5.06; N: 17.47

Example 240

To a solution of 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carbonitrile (162 mg) and thioacetamide (114 mg) in dimethylformamide (1 mL) was added 4.0 M solution of hydrogen chloride in dioxane (1 mL). The mixture was stirred for 3 hours at 100-105℃. Water was added to the reaction mixtuere to give a solid. The solid was collected by filtration, dissolved in a mixture of methanol and chloroform (5 : 95 v/v), dried over

magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by a column chromatography on silica gel (chloroform only) to give 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-1,3-thiazole-2-carbothioamide as a solid (143 mg).

m.p.: >250℃ (ethanol)

IR (KBr) : 1660, 1622, 1583 cm^{-1}

ESI/MS : 379$(M+Na)^+$, 357$(M+H)^+$

^1H NMR (DMSO-d_6, δ) : 1.24(6H, d, J=6.64 Hz), 5.13(1H, 7-plet, J=6.64 Hz), 6.88(1H, d, J=9.70 Hz), 7.14(1H, d, J=9.70 Hz), 7.42-7.50(3H, m), 7.57-7.63(2H, m), 9.91(1H, br.s), 10.27(1H, br.s)

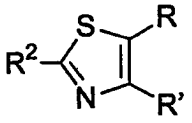
Elemental Analysis for $C_{17}H_{16}N_4OS_2 \cdot H_2O$

Calcd. C: 54.53; H: 4.84; N: 14.96

Found C: 54.30; H: 4.42; N: 14.56

CLAIMS

1. A thiazole derivative of the formula (I):



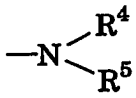
(I)

R is a 1-optionally substituted-6-oxo-1,6-dihydro-3-pyridazinyl,

R' is an optionally substituted phenyl,

R^2 is a hydrogen atom,

a group represented by the formula (i):



(i)

wherein

R^4 is hydrogen atom,

a lower alkyl group or

a lower alkenyl group, and

R^5 is hydrogen atom,

an optionally substituted lower alkyl group,

an acyl group,

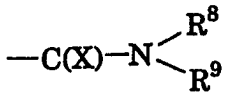
a cyclo(lower)alkyl group,

a lower alkenyl group,

an optionally substituted aryl group or

a heterocyclic group, or

a group represented by the formula (ii):



(ii)

wherein

X is an oxygen or sulfur atom,

R^8 is a hydrogen atom or

a lower alkyl group,

R^9 is a hydrogen atom,

an optionally substituted lower alkyl group,

a cyclo(lower)alkyl group,

a lower alkoxy group or

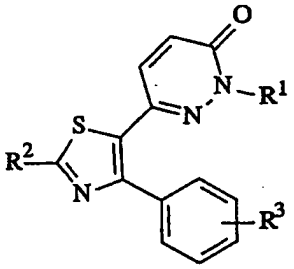
a mono- or di-lower alkylamino group or

R^8 and R^9 may combine together to form an optionally substituted saturated N-containing heterocyclic group,

or a salt thereof.

2. A thiazole derivative of Claim 1,

wherein the derivative is represented by the formula (I-1):



(I-1)

wherein

R^1 is a hydrogen atom,

an optionally substituted lower alkyl group,

a lower alkenyl group, or

a cyclo(lower)alkyl,

R^2 is as defined in Claim 1, and

R^3 is a hydrogen atom, a halogen atom, a hydroxy group, a lower alkyl group or a lower alkoxy group.

3. A compound of Claim 2,

wherein

R^1 is a hydrogen atom;

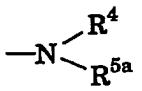
a lower alkyl group which may be substituted with lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, cyclo(lower)alkyl or aryl;

a lower alkenyl group; or

a cyclo(lower)alkyl;

R^2 is a hydrogen atom,

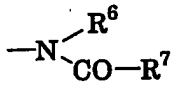
a group represented by the formula (ia):



(ia)

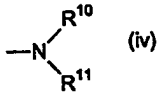
wherein

R^4 is a hydrogen atom,
a lower alkyl group or
a lower alkenyl group, and
R^{5a} is a hydrogen atom;
a lower alkyl group which may be substituted with one or more substituents selected from amino, imino, lower alkoxy, aryl and saturated or unsaturated heterocyclic group;
a lower alkyl sulfonyl group;
a cyclo(lower)alkyl group;
a lower alkenyl group;
an aryl group which may be substituted with halo(lower)alkyl or di(lower)alkylamino;
an unsaturated heterocyclic group,
a group represented by the formula (iii):



(iii)

wherein
R^6 is a hydrogen atom or
a lower alkyl group,
and
R^7 is a hydrogen atom;
a cyclo(lower)alkyl group;
a lower alkoxy group;
an aryloxy group;
a saturated or unsaturated heterocyclic group;
a mono- or di-lower alkylamino group;
an ar(lower)alkylamino group;
a lower alkyl group which may be substituted with halogen, aryl, lower alkoxy-substituted aryl, aryloxy,
or a group of the formula (iv):



(iv)

wherein

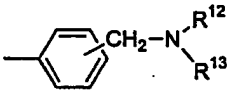
R^{10} is a hydrogen atom or a lower alkyl group,
R^{11} is a lower alkyl group, a cyclo(lower)alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a saturated or unsaturated heterocyclic(lower)alkyl group, a mono- or di-lower alkylamino(lower)alkyl group, a lower alkanoylamino(lower)alkyl group, an ar(lower)alkyl group, a hydroxy- or sulfamoyl-substituted ar(lower)alkyl group or a pyrrolidonyl(lower)alkyl group,
or R^{10} and R^{11} may combine together to form a N-containing heterocyclic group which may be substituted with lower alkyl or lower alkanoyl;

an arylamino group which may be substituted with lower alkyl;

an arylsulfonylamino group which may be substituted with lower alkyl; or

an aryl group which may be substituted with one or more of substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy, and

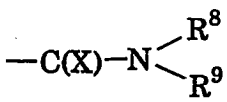
a group of the formula (v):



(v)

wherein
R^{12} is a hydrogen atom or a lower alkyl group,
R^{13} is a lower alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a saturated or unsaturated heterocyclic(lower)alkyl group, or a mono- or di-lower alkylamino(lower)alkyl group,
or R^{12} and R^{13} may combine together to form a N-containing heterocyclic group which may be substituted with lower alkyl, and

a group represented by the formula (ii):



(ii)

wherein

X is an oxygen or sulfur atom,

R^8 is a hydrogen atom or

a lower alkyl group,

R^9 is a hydrogen atom;

a lower alkyl group which may be substituted with carbamoyl, lower alkoxy, mono- or di-lower alkylamino, lower alkanoylamino, aryl, or unsubstituted or lower alkyl-substituted, saturated or unsaturated heterocyclic group;

a cyclo(lower)alkyl group;

a lower alkoxy group; or

a mono- or di-lower alkylamino group; or

R^8 and R^9 may combine together to form a saturated N-containing heterocyclic group which may be substituted with lower alkyl, lower alkanoyl, aryl or ar(lower)alkyl;

and

R^3 is a hydrogen atom, a halogen atom, a hydroxy group, a lower alkyl group or a lower alkoxy group,

or a salt thereof.

4. A compound of Claim 3

wherein

R^1 is a hydrogen atom;

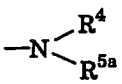
a lower alkyl group which may be substituted with lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, cyclo(lower)alkyl or phenyl;

a lower alkenyl group; or

a cyclo(lower)alkyl;

R^2 is a hydrogen atom,

a group represented by the formula (ia):



(ia)

wherein

R^4 is a hydrogen atom,

a lower alkyl group or

a lower alkenyl group, and

R^{5a} is a hydrogen atom;

a lower alkyl group which may be substituted with one or more substituents selected from amino, imino, lower alkoxy, phenyl, piperidyl, morpholinyl, pyridyl or furyl;

a lower alkyl sulfonyl group;

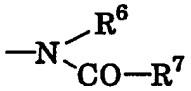
a cyclo(lower)alkyl group;

a lower alkenyl group;

a phenyl or naphthyl group which may be substituted with halo(lower)alkyl or di(lower)alkylamino;

a pyridyl group,

a group represented by the formula (iii):



(iii)

wherein

R^6 is a hydrogen atom or

a lower alkyl group,

and

R^7 is a hydrogen atom;

a cyclo(lower)alkyl group;

a lower alkoxy group;

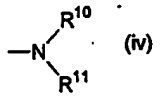
a phenoxy group;

a piperidyl, morpholinyl, pyridyl or carbazolyl group;

a mono- or di-lower alkylamino group;

a phenyl(lower)alkylamino group;

a lower alkyl group which may be substituted with halogen, phenyl, lower alkoxy-substituted phenyl, phenoxy, or a group of the formula (iv):



(iv)

wherein

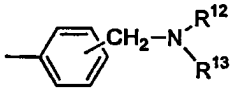
R^{10} is a hydrogen atom or a lower alkyl group,
R^{11} is a lower alkyl group, a cyclo(lower)alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a piperidyl(lower)alkyl, a morpholinyl(lower)alkyl or a pyridyl(lower)alkyl group, a mono- or di-lower alkylamino(lower)alkyl group, a lower alkanoylamino(lower)alkyl group, a phenyl(lower)alkyl group, a hydroxy- or sulfamoyl-substituted phenyl(lower)alkyl group or a pyrrolidonyl(lower)alkyl group,
or R^{10} and R^{11} may combine together to form a imidazolyl, pyrrolidinyl, piperidyl, morpholinyl or piperazinyl group which may be substituted with lower alkyl or lower alkanoyl;

an phenylamino group which may be substituted with lower alkyl;

an phenylsulfonylamino group which may be substituted with lower alkyl; or

a phenyl or naphthyl group which may be substituted with one or more of substituent(s) selected from the group consisting of halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy, and

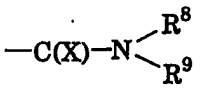
a group of the formula (v):


(v)

wherein
R^{12} is a hydrogen atom or a lower alkyl group,
R^{13} is a lower alkyl group, a hydroxy(lower)alkyl group, a lower alkoxy(lower)alkyl group, a piperidyl(lower)alkyl, a morpholinyl(lower)alkyl or a pyridyl(lower)alkyl group, or a mono- or di-lower alkylamino(lower)alkyl group,
or R^{12} and R^{13} may combine together to form a

imidazolyl, pyrrolidinyl, piperidyl, morpholinyl or piperazinyl group which may be substituted with lower alkyl, and

a group represented by the formula (ii):



(ii)

wherein

X is an oxygen or sulfur atom,

R^8 is a hydrogen atom or

a lower alkyl group,

R^9 is a hydrogen atom;

a lower alkyl group which may be substituted with carbamoyl, lower alkoxy, mono- or di-lower alkylamino, lower alkanoylamino, phenyl, morpholinyl, pyridyl or pyrazinyl which may be substituted with lower alkyl;

a cyclo(lower)alkyl group;

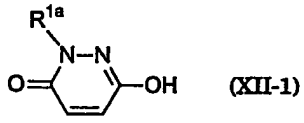
a lower alkoxy group; or

a mono- or di-lower alkylamino group; or

R^8 and R^9 may combine together to form a pyrrolidinyl, piperidyl, morpholinyl or piperazinyl group which may be substituted with lower alkyl, lower alkanoyl, phenyl or phenyl(lower)alkyl;

or a salt thereof.

5. A process for preparing a compound of the formula (XII-1):

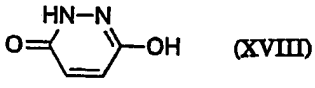


(XII-1)

or a salt thereof

which is an intermediate for preparing the compound (I) of Claim 1 comprising the steps of:

reacting a compound of the formula (XVIII):



(XVIII)

or a salt thereof with a silylating reagent, and
then with a compound of the formula (XIX) :
R^{1a}-X^1 (XIX)
or a salt thereof to give a compound of the formula (XII-1) or salt thereof wherein R^{1a} is an optionally substituted lower alkyl, lower alkenyl or cyclo(lower)alkyl group, and
X^1 is a halogen atom.

6. A process of Claim 5, wherein a solvent used for the reaction with the compound of the formula (XIX) is a solvent having a high inductivity.

7. A pharmaceutical composition comprising the compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

8. A pharmaceutical composition of Claim 7 for treating or preventing a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris.

9. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia,

electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris,
which comprises administering the compound of Claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal suffering the above disease.

10 Use of the compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt thereof as a medicament.

11. Use of the compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt thereof as an adenosine antagonist.

12 Use of the compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt thereof as an A_1 receptor and A_2 receptor dual antagonist.

13. A process for preparing a pharmaceutical composition which comprises admixing the compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

14 Use of the compound of any one of Claims 1 to 4 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the therapy of diseases on which an adenosine antagonist is therapeutically effective.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/039451 A3

(51) International Patent Classification[7]: A61K 31/501, C07D 417/04, 417/14, 237/16, A61P 25/00

(21) International Application Number: PCT/JP02/11639

(22) International Filing Date:
8 November 2002 (08.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PR 8749	8 November 2001 (08.11.2001)	AU
PR 9048	23 November 2001 (23.11.2001)	AU

(71) Applicant *(for all designated States except US)*: **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TSUTSUMI, Hideo** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **TABUCHI, Seiichiro** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **AKAHANE, Atsushi** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **YASUDA, Hironobu** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **OMORI, Hiroki** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **TEMMARU, Kiyoshi** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **ZANKA, Atsuhiko** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(74) Agent: **NOGAWA, Shintaro**; MINAMIMORIMACHI PARK BLDG., 1-3, Nishitenma 5-chome, Kita-ku, Osaka-shi, Osaka 530-0047 (JP).

(81) Designated States *(national)*: JP, US.

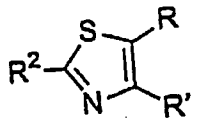
(84) Designated States *(regional)*: European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

Published:
— *with international search report*

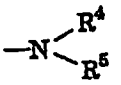
(88) Date of publication of the international search report:
25 September 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

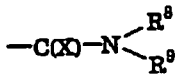
(54) Title: THIAZOLE PYRIDAZINONES AS ADENOSINE ANTAGONISTS



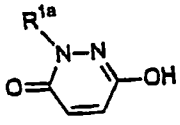
(I)



(i)



(ii)



(XII-1)

(57) Abstract: A thiazole derivative of the formula (I):wherein R is 1-optionally substituted-6-oxo-1,6-dihydro-3-pyridazinyl, R' is an optionally substituted phenyl, and R^2 is hydrogen, a group of the formula (i): wherein R^4 is hydrogen, lower alkyl or lower alkenyl, and R^5 is hydrogen, optionally substituted lower alkyl, acyl, cyclo(lower)alkyl, lower alkenyl, optionally substituted aryl or heterocyclic, or a group of the formula (ii): wherein X is oxygen or sulfur, R^8 is hydrogen or lower alkyl, R^9 is hydrogen, optionally substituted lower alkyl, cyclo(lower)alkyl, lower alkoxy or mono- or di-lower alkylamino or R^8 and R^9 may be combine together to form optionally substituted saturated N-containing heterocyclic, or a salt thereof._The compounds are useful as Adenosine antagonists. The application also discloses an improved process for the preparation of pyridazinones (XII-1)

WO 03/039451 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/11639

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/501 C07D417/04 C07D417/14 C07D237/16 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 64418 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); HENG RICHARD (FR);) 16 December 1999 (1999-12-16) cited in the application claims ---	1-4,7-14
A	WO 01 40230 A (TABUCHI SEIICHIRO ;KURODA SATORU (JP); TADA MIHO (JP); AKAHANE ATS) 7 June 2001 (2001-06-07) claims ---	1-4,7-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2003	30. 05. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/11639

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SASAKI T ET AL: "SYNTHESIS OF ADAMANTANE DERIVATIVES. LVIII. REACTION OF 1-ADAMANTYL CHLORIDE WITH SOME HETEROCYCLIC UNSATURATED SILANES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 30, no. 6, 1982, pages 2051-2060, XP001146867 ISSN: 0009-2363 page 2054; table synthesis of compound 32 ---	5,6
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1974-15003V XP002240185 -& SU 382 629 A ((ASSB) ORG SYNTH A S LATVIAN R), 30 August 1973 (1973-08-30) abstract ---	5,6
A	SCHOENBECK R: "UEBER EINIGE NEUARTIGE PYRIDAZINABKOEMMLINGE" MONATSHEFTE FUR CHEMIE, SPRINGER VERLAG. WIEN, AT, vol. 90, 1957, pages 284-296, XP001146603 ISSN: 0026-9247 cited in the application page 292, paragraph 1 ---	5,6
A	EICHENBERGER K ET AL: "HEILMITTELCHEMISCHE STUDIEN IN DER HETEROCYCLISCHEN REIHE. PYRIDAZINE V. ALKYLIERUNGEN UND UMLAGERUNGEN IN DER REIHE DES CYCLISCHEN MALEINSAEUREHYDRAZIDS" HELVETICA CHIMICA ACTA, VERLAG HELVETICA CHIMICA ACTA. BASEL, CH, vol. 37, no. 105, 1954, pages 837-848, XP009009082 ISSN: 0018-019X cited in the application page 845 last paragraph -----	5,6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/11639

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9964418 A	16-12-1999	AU 4506399 A	30-12-1999
		WO 9964418 A1	16-12-1999
WO 0140230 A	07-06-2001	AU 1309301 A	12-06-2001
		EP 1244669 A1	02-10-2002
		WO 0140230 A1	07-06-2001
SU 382629 A	25-05-1973	SU 382629 A1	25-05-1973

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/11639

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4,7-14

   Thiazole pyridazinone compounds of structure (I) and their use as adenosine antagonists

2. Claims: 5,6

   A process for the preparation of substituted pyridazinones (XII-1) characterized by the use of silylating agents